



## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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| <b>(21) International Application Number:</b> PCT/US00/01392<br><b>(22) International Filing Date:</b> 20 January 2000 (20.01.00)<br><b>(30) Priority Data:</b><br>60/121,047      22 February 1999 (22.02.99)      US<br>60/139,440      15 June 1999 (15.06.99)      US<br>09/357,743      20 July 1999 (20.07.99)      US<br><b>(71) Applicant (for all designated States except US):</b> VARIAGEN-ICS, INC. [US/US]; 60 Hampshire Street, Cambridge, MA 02139-1562 (US).<br><b>(72) Inventor; and</b><br><b>(75) Inventor/Applicant (for US only):</b> STANTON, Vincent, Jr. [US/US]; 32 Royal Road, Belmont, MA 02173 (US).<br><b>(74) Agents:</b> WARBURG, Richard, J. et al.; Lyon & Lyon LLP, 633 West Fifth Street, Suite 4700, Los Angeles, CA 90071-2066 (US). |           | <b>(81) Designated States:</b> AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).<br><br><b>Published</b><br><i>Without international search report and to be republished upon receipt of that report.</i> |
| <b>(54) Title:</b> GENE SEQUENCE VARIATIONS WITH UTILITY IN DETERMINING THE TREATMENT OF DISEASE<br><b>(57) Abstract</b><br><p>The present disclosure describes the use of genetic variance information for genes involved in gene pathways in the selection of effective methods of treatment of a disease or condition. The variance information is indicative of the expected response of a patient to a method of treatment. Methods of determining relevant variance information and additional methods of using such variance information are also described.</p>                                                                                                                                                                                                   |           |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |

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## **DESCRIPTION**

### **GENE SEQUENCE VARIATIONS WITH UTILITY IN DETERMINING THE TREATMENT OF DISEASE**

#### **BACKGROUND OF THE INVENTION**

This application concerns the field of mammalian therapeutics and the selection of therapeutic regimens utilizing host genetic information, including gene sequence variances within the human genome in human populations.

The information provided below is not admitted to be prior art to the present invention, but is provided solely to assist the understanding of the reader.

Many drugs or other treatments are known to have highly variable safety and efficacy in different individuals. A consequence of such variability is that a given drug or other treatment may be effective in one individual, and ineffective or not well-tolerated in another individual. Thus, administration of such a drug to an individual in whom the drug would be ineffective would result in wasted cost and time during which the patient's condition may significantly worsen. Also, administration of a drug to an individual in whom the drug would not be tolerated could result in a direct worsening of the patient's condition and could even result in the patient's death.

For some drugs, over 90% of the measurable variation in selected pharmacokinetic parameters has been shown to be heritable. For a limited number of drugs, geneDNA sequence variances have been identified in specific genes that are involved in drug action or metabolism, and these variances have been shown to account for the variable efficacy or safety of the drugs in different individuals. As the sequence of the human genome is completed, and as additional human gene sequence variances are identified, the power of genetic methods for predicting drug response will further increase.

In this invention, we address the difficulties that arise in treating the following disease categories: 1) neurological and psychiatric disease; 2) pharmacokinetic and dynamic indices including efficacy, absorption, distribution, metabolism, and excretion, as well as safety and toxicity parameters; 3) inflammation and immune disease; 4) endocrine and metabolic disease; 5) cardiovascular and renal disease; and 6) cancer.

#### **Neurological and Psychiatric Disease**

Diseases of the central nervous system (CNS) present unique medical challenges to clinicians, patients, and caregivers. These diseases often progress to severely debilitating conditions. Further, the efficacy of available treatments is limited and there are serious, mostly unpredictable, side effects associated with some drugs. The progressive nature of neurological and psychiatric disease makes the passage of time a crucial issue in the treatment process. Specifically, selection of optimal treatment for neurological and psychiatric diseases is complicated by the fact that it often takes weeks or months to determine if a given therapy is symptomologyproducing a measurable benefit. Thus the current empirical approach to prescribing pharmacotherapy, in which each course of treatment for a given patient is a small experiment, is unsatisfactory from both a medical and economic perspective. Even when an effective treatment is ultimately identified, it often follows a period of ineffective or suboptimal treatment.

#### Pharmacokinetic and Pharmacodynamic Effects

The efficacy of a drug is a function of both pharmacodynamic effects and pharmacokinetic effects, or bioavailability. In the present invention, interpatient variability in drug safety, tolerability and efficacy are discussed in terms of the genetic determinants of interpatient variation in absorption, distribution, metabolism, and excretion, i.e. pharmacokinetic parameters.

Adverse drug reactions are a principal cause of the low success rate of drug development programs (less than one in four compounds that enters human clinical testing is ultimately approved for use by the US Food and Drug Administration (FDA)). Adverse drug reactions can be categorized as 1) mechanism based reactions and 2) idiosyncratic, "unpredictable" effects apparently unrelated to the primary pharmacologic action of the compound. Although some side effects appear shortly after administration, in some instances side effects appear only after a latent period. Adverse drug reactions can also be categorized into reversible and irreversible effects. The methods of this invention are useful for identifying the genetic basis of both mechanism based and 'idiosyncratic' toxic effects, whether reversible or not. Methods for identifying the genetic sources of interpatient variation in efficacy and mechanism based toxicity may be initially directed to analysis of genes affecting pharmacokinetic parameters, while the genetic causes of idiosyncratic adverse drug reactions are more likely to be attributable to genes affecting variation in pharmacodynamic responses or immunological responsiveness.

Absorption is the first pharmacokinetic parameter to consider when determining the causes of intersubject variation in drug response. The relevant genes depend on the route of administration of the compound being evaluated. For

orally administered drugs the major steps in absorption may occur during exposure to salivary enzymes in the mouth, exposure to the acidic environment of the stomach, exposure to pancreatic digestive enzymes and bile in the small intestine, exposure to enteric bacteria and exposure to cell surface proteins throughout the gastrointestinal tract. For example, uptake of a drug that is absorbed across the gastrointestinal tract by facilitated transport may vary on account of allelic variation in the gene encoding the transporter protein. Many drugs are lipophilic (a property which promotes passive movement across biological membranes). Variation in levels of such drugs may depend, for example, on the enterohepatic circulation of the drug, which may be affected by genetic variation in liver canalicular transporters, or intestinal transporters; alternatively renal reabsorption mechanisms may vary among patients as a consequence of gene sequence variances. If a compound is delivered parenterally then absorption is not an issue, however transcutaneous administration of a compound may be subject to genetically determined variation in skin absorptive properties.

Once a drug or candidate therapeutic intervention is absorbed, injected or otherwise enters the bloodstream it is distributed to various biological compartments via the blood. The drug may exist free in the blood, or, more commonly, may be bound with varying degrees of affinity to plasma proteins. One classic source of interpatient variation in drug response is attributable to amino acid polymorphisms in serum albumin, which affect the binding affinity of drugs such as warfarin. Consequent interpatient variation in levels of free warfarin have a significant effect on the degree of anticoagulation. From the blood a compound diffuses into and is retained in interstitial and cellular fluids of different organs to different degrees. Interpatient variation in the levels of a drug in different anatomical compartments may be attributable to variation in the genetically encoded chemical environment of those tissues (cell surface proteins, matrix proteins, cytoplasmic proteins and other factors)

Once absorbed by the gastrointestinal tract, compounds encounter detoxifying and metabolizing enzymes in the tissues of the gastrointestinal system. Many of these enzymes are known to be polymorphic in man and account for well studied variation in pharmacokinetic parameters of many drugs. Subsequently compounds enter the hepatic portal circulation in a process commonly known as first pass. The compounds then encounter a vast array of xenobiotic detoxifying mechanisms in the liver, including enzymes which are expressed solely or at high levels only in liver. These enzymes include the cytochrome P450s, glucuronyltransferases, sulfotransferases, acetyltransferases, methyltransferases, the glutathione conjugating system, flavine monooxygenases, and other enzymes known

in the art. Polymorphisms have been detected in all of these metabolizing systems, however the genetic factors responsible for intersubject variation have only been partially identified, and in some cases not yet identified at all. Biotransformation reactions in the liver often have the effect of converting lipophilic compounds into hydrophilic molecules which are then more readily excreted. Variation in these conjugation reactions may affect half-life and other pharmacokinetic parameters. It is important to note that metabolic transformation of a compound not infrequently gives rise to a second or additional compounds that have biological activity greater than, less than, or different from that of the parent compound. Metabolic transformation may also be responsible for producing toxic metabolites.

Biotransformation reactions can be divided into two phases. Phase I are oxidation-reduction reactions and phase II are conjugation reactions. The enzymes involved in both of these phases are located predominantly in the liver, however biotransformation can also occur in the kidney, gastrointestinal tract, skin, lung and other organs. Phase I reactions occur predominantly in the endoplasmic reticulum, while phase II reactions occur predominantly in the cytosol. Both types of reactions can occur in the mitochondria, nuclear envelope, or plasma membrane. One skilled in the art can, for some compounds, make reasonable predictions concerning likely metabolic systems given the structure of the compound. Experimental means of assessing relevant biotransformation systems are also described.

#### Drug-Induced Disease, Disorders or Toxicities

Drug-induced disease or toxicity presents a unique series of challenges to drug developers, as these reactions are often not predictable from preclinical studies and may not be detected in early clinical trials involving small numbers of subjects. When such effects are detected in later stages of clinical development they often result in termination of a drug development program because, until now, there have been no effective tools to seek the determinants of such reactions. When a drug is approved despite some toxicity its clinical use is frequently severely constrained by the possible occurrence of adverse reactions in even a small group of patients. The likelihood of such a compound becoming first line therapy is small (unless there are no competing products). Thus clinical trials that lead to detection of genetic causes of adverse events and subsequently to the creation of genetic tests to identify and screen out patients susceptible to such events have the potential to (i) enable approval of compounds for genetically circumscribed populations or (ii) enable repositioning of approved compounds for broader clinical use.

Similarly, many compounds are not approved due to unimpressive efficacy. The identification of genetic determinants of pharmacokinetic variation may lead to identification of a genetically defined population in whom a significant response is

occurring. Approval of a compound for this population, defined by a genetic diagnostic test, may be the only means of getting regulatory approval for a drug. As healthcare becomes increasingly costly, the ability to allocate healthcare resources effectively becomes increasingly urgent. The use of genetic tests to develop and rationally administer medicines represents a powerful tool for accomplishing more cost effective medical care.

#### Inflammation and Immune Disease

In this application, we further address the difficulties that arise in treating inflammatory diseases and other diseases in which modulation of immunologic function provides the basis for therapeutic intervention, including, for example, diseases treated with antiinflammatory, analgesic or antipyretic drugs as well as autacoids, eicosanoids, interleukins, cytokines or their agonists or antagonists. Diseases or conditions involving the inflammatory response or immune system constitute a complex and heterogeneous group of diseases, involving all organ systems from the central nervous system and the circulatory system to the viscera and skin. The diseases may be acute or chronic, or may have an acute stage which later progresses to a chronic condition, or may exhibit a waxing and waning pattern of flare ups and remissions. Due to their wide anatomical distribution, this group of diseases can (collectively) lead to impairment of a wide range of essential physiological functions. The unifying theme in the treatment of these diseases is the modulation of inflammatory mediators or immune function.. The evaluation of long term response to therapy is, for many of these diseases, the most important index of treatment efficacy, due to the progressive nature of inflammatory or immunological diseases. Since it is often difficult to assess the long term effects of treatment over a short observation period (particularly for diseases with a waxing and waning pattern) there is considerable utility in a genetic test that can predict long term outcomes. Many treatments for diseases with significant inflammatory or immunological components are quite costly.

#### Endocrine and Metabolic Disease

The endocrine system encompasses a number of organs that collectively regulate a wide array of physiologic, metabolic and developmental processes including metabolism, growth, reproduction, development, senescence, behavior, including adaptation to stress, the composition of intracellular and extracellular fluids (e.g. salt and water balance), digestion and wound healing, among other processes. The endocrine organs include the hypothalamus, pituitary gland, thyroid, parathyroid, endocrine pancreas, adrenal gland, gonads, and cells of the gastrointestinal tract, liver, kidneys, heart, pineal gland, and placenta.

Endocrine signals can be classified as autocrine, paracrine, or endocrine depending on the distance over which a signal must be transmitted. Endocrine signals are transmitted by hormones including peptides, proteins, steroids and small molecule neurotransmitters. The hormones carry biological signals to target cells. Receptors located on the cell surface (membrane bound) activate intracellular second messenger systems to ultimately alter intracellular metabolism, physiology and cell function. Second messengers systems include adenylate cyclase, guanylate cyclase, phospholipases, and kinases. Some membrane receptors interact with GTP-binding proteins; others produce intracellular signals themselves (for example receptors with tyrosine kinase domains). Other receptors are located intracellularly (for example steroid hormone receptors) and the hormone-receptor complex acts to stimulate intracellular processes such as gene transcription.

Regulation in the endocrine system occurs via a complex system of signals transmitted by hormones, neurotransmitters and other small molecules. These signals participate in feedback loops, recruitment of coordinate responses, and cycles or rhythms. The feedback loops function to coordinately stimulate or terminate hormone signals. In this way, communication occurs between cells or tissues that are physically separated. For example, a peripheral endocrine gland may release hormones in response to centrally produced stimulatory hormones, with the peripherally produced substances feeding back on the central nervous system to decrease production of the stimulatory signal. In other systems the action of multiple hormones must be coordinated. For example, female reproductive system requires hypothalamic, pituitary and ovarian signals and also includes effector targets in the breasts, uterus, and vagina. Endocrine signalling systems that are regulated in a coordinated fashion include, for example, the hypothalamic-pituitary-gonadal axis, the hypothalamic-pituitary-adrenal corticotroph axis and the hypothalamic-pituitary-thyroid axis. Within the endocrine system there is integration of endocrine responses that are grouped as.

Many hormones are extensively processed prior to secretion. For example in the posterior pituitary gland, a hormone gene encodes a preprohormone that contains several proteins or peptides in contiguous alignment that requires modification prior to becoming an active signaling hormone. The preprohormone after nascent ribosome synthesis then is cut by specific or nonspecific processing proteins to a smaller prohormone within the Golgi apparatus, that then is glycosylated and placed into a secretory granule. Within the secretory granule, the prohormone is then further processed into the active hormone. The active hormone is secreted as a response to physiologic signals and renders the specific biologic function at the target organ or tissue. In this complex protein processing mechanism, there is the

possibility of secreting more than one hormones or signaling peptides in the same secretory granule, and as described above, can lead to the delivery of multiple signals to one or more target tissues.

Assessment of endocrine function can be conducted by quantitation of circulating hormones and metabolic products, stimulation and suppression tests, and anatomic assessment. Aberrations of endocrine disease, disorder, or dysfunction manifests clinically as either a deficiency or a excess of 1) endocrine function or 2) hormone production, or may be the result of loss of 1) feedback loops, 2) recruitment of hormone signals, or 3) cycles or pulsatile hormone secretion. Lastly, there may be genetic determinants of endocrine disease, for example mutations or polymorphisms in biosynthetic enzymes, hormone receptors, peptide hormone or small molecules, immune surveillance, tumor suppressor genes, and others such that these changes or differences from normally occurring proteins or molecules alters their functional pattern and the clinical manifestation is then characteristic of endocrine disease.

Endocrine or metabolic disease provide a unique series of complications for clinicians, patients, and care givers; the diseases often progress rapidly and disrupts a vast number of major life functions. The progressive nature of these disease syndromes makes the passage of time a crucial issue in the treatment process. Treatment choices for endocrine or metabolic disorders and their associated pathologies, particularly those affecting major organs, e.g. coronary, hepatic, renal systems, are often complicated by the fact that it often takes a significant period of treatment to determine if a given therapy is effective. Accordingly, treatment with the most effective drug or drugs is often delayed while the disease continues to progress. A method that would allow one to predict which patients will respond to a specific therapy would provide physical and psychological benefits. As healthcare becomes increasingly inaccessible, the ability to allocate healthcare resources effectively also becomes more important.

#### Cardiovascular and Renal Disease

In this application, we address the difficulties that arise in treating cardiovascular and renal diseases, describe methods to enable more effective use of available therapeutics, and methods for developing new therapies. Diseases of the cardiovascular and renal systems often progress, over periods of years to decades, to severely debilitating and life threatening conditions. The efficacy of available treatments is limited and there are side effects associated with many of the drugs used to treat these diseases. Due to the progressive nature of many cardiovascular and renal diseases it is of great importance to select an effective therapeutic regimen at the time of diagnosis. The effectiveness of therapy is often

assessed by short-term measurements of surrogate markers (e.g. blood pressure, blood lipid levels or blood clotting parameters), however the important endpoints (e.g. myocardial infarction, thromboembolism, renal failure) occur (or are prevented) over the long term. Thus, the tools for selecting optimal therapy for individual patients are currently limited, and as a result some patients receive treatment from which they do not benefit, while other patients may not receive treatment that would produce significant benefit. The current empirical approach to prescribing pharmacotherapy, in which each course of treatment for a given patient is a small experiment (e.g. the selection of effective therapy for blood pressure control), is unsatisfactory from both a medical and economic perspective. Even when an effective treatment is ultimately identified, it often follows a period of ineffective or suboptimal treatment. Methods that would help caregivers predict which patients will exhibit beneficial therapeutic responses to which medications would provide both medical and economic benefits. As healthcare becomes increasingly costly, the ability to rationally allocate healthcare expenditures, and in particular pharmacy resources, becomes increasingly important. The methods of this invention provide a basis for selecting more efficacious pharmacotherapy of cardiovascular and renal diseases.

#### Neoplastic Disorders

In this application, we also address the difficulties that arise in treating neoplastic disease. Due to the often rapid progression and life-threatening nature of neoplastic diseases, both early detection and effective treatment are essential. Clearly, there would be great benefit to patients if therapies that will ultimately prove to be ineffective in curbing the progression of disease could be avoided initially, given the cost and often noxious side effects associated with such therapies. Many current therapies for neoplastic disease are targeted against processes such as cell growth and division that occur in both normal and cancerous tissues (albeit at different rates), resulting in pronounced toxicity to normal tissues. Toxic reactions are the most severe in tissues which proliferate rapidly, such as gastrointestinal epithelium and hematopoietic tissues, however serious adverse reactions also occur in other organs occasionally, including heart, kidney, liver, lung and brain. As a consequence of the narrow therapeutic index associated with most antineoplastic treatments, skillful choice of treatments (including the agents used and the dose, if the treatment involves drugs) must be made by the attending physician based not only upon the type of cancer and stage of dissemination, but on a number of additional factors including status of the patient's hematopoietic and myelogenic tissues, hepatic and renal function and age. Knowledge of genetic factors which would impact the choice of treatment based either on optimizing efficacy or



minimizing toxicity would greatly benefit cancer patients, because the efficacy of available treatments is limited and there are serious, mostly unpredictable, side effects associated with some drugs. Thus a method that would allow one to predict which patients will exhibit beneficial therapeutic response to a specific medication with minimal adverse effects (often less than half of treated patients, and not infrequently one quarter or less) would provide physical, psychological, and societal benefits. Using such a method, those patients not likely to benefit from aggressive treatment could be offered palliative care. Tumor growth exhibits gompertzian kinetics—growth rate declines with increasing tumor burden. Since chemotherapies are frequently most effective against rapidly growing tumors (low tumor burden), it is imperative that treatment begin immediately after disease detection and that the tumor responds to first-line therapy. Further, selection of optimal treatment for a neoplastic disease is complicated by the fact that it often takes weeks or months to determine if a given therapy is producing a measurable benefit. Thus the current empirical approach to prescribing pharmacotherapy, in which each course of treatment for a given patient is a small experiment, is unsatisfactory from both a medical and economic perspective. Even when an effective treatment is ultimately identified, it often follows a period of ineffective or suboptimal treatment.

Neoplastic diseases are related by the fact that they result from the unchecked growth of a previously normal cell, generally thought to be precipitated by one or more mutations in its genetic material. Cancerous cells can undergo gene loss and duplication to become aneuploid or partially polyploid, but usually retain some of the characteristics of their source tissue. Neoplastic cells differ in their ability to form solid tumors, to disseminate from the original site of tumor formation and form metastases, and in their requirements for growth factors, which can include steroid hormones in the case of carcinomas of the prostate or breast. Tumor cells, while having sustained alterations to their genetic material that lead either to a loss of growth inhibition or to a gain of growth function, still produce all the enzymes and other macromolecules required for cell viability. In this regard, they are extremely similar to non-cancerous tissue, and selective poisoning of tumor tissue over normal tissue has for the most part proven elusive. Current chemotherapies mainly target normal cell functions including DNA replication, cell division, RNA transcription, and nucleotide metabolism and are often associated with nausea and vomiting, diarrhea, hair loss, anemia, immune suppression (and consequent increased risk of infection), as well as a host of less common side effects including pulmonary fibrosis, and cardiac, hepatic and renal toxicity. Radiation therapy, often used in the treatment of inoperable tumors such as various brain and laryngeal tumors (but also widely used to treat breast cancer in patients who have had

lumpectomies), has the advantage that it can be restricted to a small area, especially when used in conjunction with tissue selective radiosensitizers or radioprotectants. Radiation therapy also targets rapidly proliferating tissues and shares many of the side effects of cytotoxic agents. Minimization of severe toxic reactions to cancer therapy through knowledge of genetic variances in normal tissue that could impact either drug metabolism or cellular repair processes would be an invaluable addition to cancer therapy.

Accordingly, a method that would help caregivers predict which patients will exhibit beneficial therapeutic responses to a specific which medication or medications would provide both medical and economic benefits. As healthcare becomes increasingly costly, the ability to rationally allocate healthcare expenditures, and in particular pharmacy resources, also becomes increasingly important.

## SUMMARY OF THE INVENTION

The present invention is concerned generally with the field of identifying an appropriate treatment regimen for a neurological or psychiatric disease, drug-induced disease or disorders, endocrine or metabolic disease, inflammatory disease (or a disease in which modulation of the inflammatory response or the immune system is being tested for therapeutic effect), and cardiovascular and renal diseases, based upon genotype in mammals, particularly in humans. The present invention is additionally concerned generally with the field of pharmacology, specifically pharmacokinetics and toxicology, and more specifically with identifying and predicting inter-patient differences in response to drugs in order to achieve superior efficacy and safety in selected patient populations.

It is further concerned with the genetic basis of inter-patient variation in response to therapy, including drug therapy, and with methods for determining and exploiting such differences to improve medical outcomes. Specifically, this invention describes the identification of genes and gene sequence variances useful in the field of therapeutics for optimizing efficacy and safety of drug therapy by allowing prediction of pharmacokinetic and/or toxicologic behavior of specific drugs in specific patients. Relevant pharmacokinetic processes include absorption, distribution, metabolism and excretion. Relevant toxicological processes include both dose related and idiosyncratic adverse reactions to drugs, including, for example, hepatotoxicity, blood dyscrasias and immunological reactions.

It is further concerned with the genetic basis of inter-patient variation in response to therapy, including drug therapy. Specifically, this invention describes the identification of gene sequence variances useful in the field of therapeutics for optimizing efficacy and safety of drug therapy. These variances may be useful  
5 either during the drug development process or in guiding the optimal use of already approved compounds. DNA sequence variances in candidate genes (i.e. genes that may plausibly affect the action of a drug) are tested in clinical trials, leading to the establishment of diagnostic tests useful for improving the development of new pharmaceutical products and/or the more effective use of existing pharmaceutical  
10 products. Methods for identifying genetic variances and determining their utility in the selection of optimal therapy for specific patients are also described. In general, the invention relates to methods for identifying patient population subsets that respond to drug therapy with either therapeutic benefit or side effects (i.e. symptomatology prompting concern about safety or other unwanted signs or  
15 symptoms).

This broad range of pharmacological interactions with receptors, transporters, enzymes and other proteins which are differentially expressed in different populations of cells, e.g., in the CNS, has implications for the design of experiments to identify genetic determinants of drug response. In particular, because  
20 of the broad pharmacological interactions of compounds being developed as CNS drugs it may be necessary to study the effect of DNA sequence variances in a number of different sets of genes (belonging to different biochemical pathways) in order to identify a sequence variance or set of variances responsible for interpatient variation in drug response. Methods are described herein for identifying relevant  
25 DNA sequence variances and associating them with drug response phenotypes.

While the complexity of CNS physiology creates challenges for pharmacogenetic studies, it is also the case that the pharmacological treatment of CNS diseases provides broad scope for the methods of this invention, because (i) the hereditary component of many CNS diseases is well established, indicating a major  
30 role of genetic (as opposed to environmental) factors in disease etiology, (ii) the molecular pharmacology of CNS drugs is generally well understood, providing a rational basis for selecting genes for pharmacogenetic investigation (iii) the heterogeneous responses of patients to CNS drugs suggests that the factors governing response extend beyond presently understood mechanisms; genetic  
35 variation can affect virtually all aspects of pharmacology, and is, for the reasons cited above, likely to account for much of the heterogeneity in drug response. In this application we describe methods for improving the treatment of neurological and psychiatric diseases, movement disorders, neurodegenerative diseases, disorders of

sensation, and cerebrovascular diseases. Specifically, we address the treatment of migraine, pain, epilepsy, schizophrenia, stroke, depression, anxiety, spasticity, Parkinson's disease, dementia, demyelinating disease, amyotrophic lateral sclerosis, and Huntington's disease.

5           Specifically, this invention describes the identification of genes and gene sequence variances useful in the field of therapeutics for optimizing efficacy and safety of drug therapy by allowing prediction of pharmacokinetic and/or toxicologic behavior of specific drugs in specific patients. Relevant pharmacokinetic processes include absorption, distribution, metabolism and excretion. Relevant toxicological  
10           processes include both dose related and idiosyncratic adverse reactions to drugs, including, for example, hepatotoxicity, blood dyscrasias and immunological reactions.

          The invention also describes methods for establishing diagnostic tests useful in (i) the development of, (ii) obtaining regulatory approval for and (iii) safe and  
15           efficacious clinical use of pharmaceutical products. These variances may be useful either during the drug development process or in guiding the optimal use of already approved compounds. DNA sequence variances in candidate genes (i.e. genes that may plausibly affect the action of a drug) are tested in clinical trials, leading to the establishment of diagnostic tests useful for improving the development of new  
20           pharmaceutical products and/or the more effective use of existing pharmaceutical products. Methods for identifying genetic variances and determining their utility in the selection of optimal therapy for specific patients are also described. In general, the invention relates to methods for identifying and dealing effectively with the genetic sources of interpatient variation in drug response, including both variable  
25           efficacy as determined by pharmacokinetic variability and variable toxicity as determined by pharmacokinetic factors or by other genetic factors (e.g. factors responsible for idiosyncratic drug response).

          This application is directed also to diseases in which abnormal function of the immune system or the inflammatory response is part of the disease process, or in  
30           which modulation of immune or inflammatory function is being tested as a therapeutic intervention. Specifically we address the treatment of arthritis, chronic obstructive pulmonary disease, autoimmune disease, transplantation, pain associated with inflammation, psoriasis, atherosclerosis, asthma, inflammatory bowel disease, and hepatitis.

35           In this application we further describe methods for improving the treatment of endocrine and metabolic diseases. Specifically, we address the treatment of diabetes mellitus and the related metabolic syndrome X, diabetes insipidus, obesity, contraception and infertility, osteoporosis, acne, and alopecia. The methods of this

invention are also relevant to devising effective genetic approaches to drug development for endocrine diseases of pituitary, thyroid, parathyroid, adrenal, gonads and secondary sex tissues.

While the complexity of cardiovascular and renal physiology creates  
5 challenges for pharmacogenetic studies (e.g. selecting the right genes to study, selecting the relevant DNA sequence variances within those genes, constructing sound genetic statistical tests, etc.), it is also the case that the pharmacological treatment of cardiovascular and renal diseases provides broad scope for the methods of this invention, because (i) the hereditary component of many cardiovascular and  
10 renal diseases is well established, indicating a major role of genetic (as opposed to environmental) factors in disease etiology, (ii) the molecular pharmacology of cardiovascular and renal drugs is generally well understood, providing a rational basis for selecting genes for pharmacogenetic investigation (iii) the heterogeneous responses of patients to cardiovascular and renal drugs suggests that the factors  
15 governing response extend beyond presently understood mechanisms; genetic variation can affect virtually all aspects of pharmacology, and are, for the reasons cited above, likely to account for much of the heterogeneity in drug response. In this application we describe methods for improving the treatment of cardiovascular and renal diseases. Specifically, we address the treatment of anemia, angina (including  
20 coronary artery atherosclerosis), arrhythmias, hypertension, hypotension, myocardial ischemia, heart failure, thrombosis, renal diseases, restenosis, and peripheral vascular disease (including atherosclerosis). The methods of this invention are also relevant to devising effective genetic approaches to drug development for other cardiovascular and renal diseases.

25 Described in the Examples and Tables are pathways, genes and gene sequence variances useful in the genetic analysis of treatment response for each of these diseases, and exemplary compounds being developed to treat each of these diseases, the use of which may be improved by genetic analysis of the type described herein.

30 The inventors have determined that the identification of gene sequence variances in genes that may be involved in drug action are useful for determining whether genetic variances account for variable drug efficacy and safety and for determining whether a given drug or other therapy may be safe and effective in an individual patient. Provided in this invention are identifications of genes and  
35 sequence variances which can be useful in connection with predicting differences in response to treatment and selection of appropriate treatment of a disease or condition. A target gene and variances are useful, for example, in pharmacogenetic association studies and diagnostic tests to improve the use of certain drugs or other

therapies including, but not limited to, the drug classes and specific drugs identified in the 1999 Physicians' Desk Reference (53rd edition), Medical Economics Data, 1998, the 1995 United States Pharmacopeia XXIII National Formulary XVIII, Interpharm Press, 1994, Tables 24-68 or other sources as described below.

5           The terms "disease" or "condition" are commonly recognized in the art and designate the presence of signs and/or symptoms in an individual or patient that are generally recognized as abnormal. Diseases or conditions may be diagnosed and categorized based on pathological changes. Signs may include any objective evidence of a disease such as changes that are evident by physical examination of a patient or the results of diagnostic tests which may include, among others, laboratory tests to determine the presence of DNA sequence variances or variant forms of certain genes in a patient. Symptoms are subjective evidence of disease or a patients condition, i.e. the patients perception of an abnormal condition that differs from normal function, sensation, or appearance, which may include, without limitations, physical disabilities, morbidity, pain, and other changes from the normal condition experienced by an individual. Various diseases or conditions include, but are not limited to; those categorized in standard textbooks of medicine including, without limitation, textbooks of nutrition, allopathic, homeopathic, and osteopathic medicine. In certain aspects of this invention, the disease or condition is selected from the group consisting of the types of diseases listed in standard texts such as Harrison's Principles of Internal Medicine (14th Ed) by Anthony S. Fauci, Eugene Braunwald, Kurt J. Isselbacher, et al. (Editors), McGraw Hill, 1997, or Robbins Pathologic Basis of Disease (6th edition) by Ramzi S. Cotran, Vinay Kumar, Tucker Collins & Stanley L. Robbins, W B Saunders Co., 1998, or the Diagnostic and Statistical Manual of Mental Disorders: DSM-IV (4<sup>th</sup> edition), American Psychiatric Press, 1994, or other texts described below. Examples for this invention include, neoplastic disorders such as cancer, amyotrophic lateral sclerosis, anxiety, dementia, depression, epilepsy, Huntington's disease, migraine, demyelinating disease, multiple sclerosis, pain, Parkinson's disease, schizophrenia, spasticity, psychoses, and stroke, drug-induced diseases, disorders, or toxicities consisting of blood dyscrasias, cutaneous toxicities, systemic toxicities, central nervous system toxicities, hepatic toxicities, cardiovascular toxicities, pulmonary toxicities, and renal toxicities, arthritis, chronic obstructive pulmonary disease, autoimmune disease, transplantation, pain associated with inflammation, psoriasis, atherosclerosis, asthma, inflammatory bowel disease, and hepatitis, diabetes mellitus, metabolic syndrome X, diabetes insipidus, obesity, contraception, infertility, hormonal insufficiency related to aging, osteoporosis, acne, alopecia, adrenal dysfunction, thyroid dysfunction, and parathyroid dysfunction, anemia,

angina, arrhythmia, hypertension, hypothermia, ischemia, heart failure, thrombosis, renal disease, restenosis, and peripheral vascular disease

In connection with the methods of this invention, unless otherwise indicated, the term "suffering from a disease or condition" means that a person is either  
5 presently subject to the signs and symptoms, or is more likely to develop such signs and symptoms than a normal person in the population. Thus, for example, a person suffering from a condition can include a developing fetus, a person subject to a treatment or environmental condition which enhances the likelihood of developing the signs or symptoms of a condition, or a person who is being given or will be  
10 given a treatment which increase the likelihood of the person developing a particular condition. For example, tardive dyskinesia is associated with long-term use of anti-psychotics; dyskinesias, paranoid ideation, psychotic episodes and depression have been associated with use of L-dopa in Parkinson's disease; (and dizziness, diplopia, ataxia, sedation, impaired mentation, weight gain, and other undesired effects have  
15 been described for various anticonvulsant therapies. Thus, methods of the present invention which relate to treatments of patients (e.g., methods for selecting a treatment, selecting a patient for a treatment, and methods of treating a disease or condition in a patient) can include primary treatments directed to a presently active disease or condition, secondary treatments which are intended to cause a biological  
20 effect relevant to a primary treatment, and prophylactic treatments intended to delay, reduce, or prevent the development of a disease or condition, as well as treatments intended to cause the development of a condition different from that which would have been likely to develop in the absence of the treatment.

The term "therapy" refers to a process which is intended to produce a  
25 beneficial change in the condition of a mammal, e.g., a human, often referred to as a patient. A beneficial change can, for example, include one or more of: restoration of function, reduction of symptoms, limitation or retardation of progression of a disease, disorder, or condition or prevention, limitation or retardation of deterioration of a patient's condition, disease or disorder. Such therapy can involve,  
30 for example, nutritional modifications, administration of radiation, administration of a drug, behavioral modifications, and combinations of these, among others.

The term "drug" as used herein refers to a chemical entity or biological product, or combination of chemical entities or biological products, administered to a person to treat or prevent or control a disease or condition. The chemical entity or  
35 biological product is preferably, but not necessarily a low molecular weight compound, but may also be a larger compound, for example, an oligomer of nucleic acids, amino acids, or carbohydrates including without limitation proteins, oligonucleotides, ribozymes, DNazymes, glycoproteins, lipoproteins, and

modifications and combinations thereof. A biological product is preferably a monoclonal or polyclonal antibody or fragment thereof such as a variable chain fragment; cells; or an agent or product arising from recombinant technology, such as, without limitation, a recombinant protein, recombinant vaccine, or DNA construct developed for therapeutic, e.g., human therapeutic, use. The term "drug" may include, without limitation, compounds that are approved for sale as pharmaceutical products by government regulatory agencies (e.g., U.S. Food and Drug Administration (USFDA or FDA), European Medicines Evaluation Agency (EMEA), and a world regulatory body governing the International Conference of Harmonization (ICH) rules and guidelines), compounds that do not require approval by government regulatory agencies, food additives or supplements including compounds commonly characterized as vitamins, natural products, and completely or incompletely characterized mixtures of chemical entities including natural compounds or purified or partially purified natural products. The term "drug" as used herein is synonymous with the terms "medicine", "pharmaceutical product", or "product". Most preferably the drug is approved by a government agency for treatment of a specific disease or condition.

A "low molecular weight compound" has a molecular weight  $<5,000$  Da, more preferably  $<2500$  Da, still more preferably  $<1000$  Da, and most preferably  $<700$  Da.

Those familiar with drug use in medical practice will recognize that regulatory approval for drug use is commonly limited to approved indications, such as to those patients afflicted with a disease or condition for which the drug has been shown to be likely to produce a beneficial effect in a controlled clinical trial. Unfortunately, it has generally not been possible with current knowledge to predict which patients will have a beneficial response, with the exception of certain diseases such as bacterial infections where suitable laboratory methods have been developed. Likewise, it has generally not been possible to determine in advance whether a drug will be safe in a given patient. Regulatory approval for the use of most drugs is limited to the treatment of selected diseases and conditions. The descriptions of approved drug usage, including the suggested diagnostic studies or monitoring studies, and the allowable parameters of such studies, are commonly described in the "label" or "insert" which is distributed with the drug. Such labels or inserts are preferably required by government agencies as a condition for marketing the drug and are listed in common references such as the Physicians Desk Reference (PDR). These and other limitations or considerations on the use of a drug are also found in medical journals, publications such as pharmacology, pharmacy or medical



textbooks including, without limitation, textbooks of nutrition, allopathic, homeopathic, and osteopathic medicine.

Many widely used drugs are effective in a minority of patients receiving the drug, particularly when one controls for the placebo effect. For example, the PDR shows that about 45% of patients receiving Cognex (tacrine hydrochloride) for Alzheimer's disease show no change or minimal worsening of their disease, as do about 68% of controls (including about 5% of controls who were much worse). About 58% of Alzheimer's patients receiving Cognex were minimally improved, compared to about 33% of controls, while about 2% of patients receiving Cognex were much improved compared to about 1% of controls. Thus a tiny fraction of patients had a significant benefit. Response to treatments for amyotrophic lateral sclerosis are likewise minimal.

Thus, in a first aspect, the invention provides a method for selecting a treatment for a patient suffering from a disease or condition by determining whether or not a gene or genes in cells of the patient (in some cases including both normal and disease cells, such as cancer cells) contain at least one sequence variance which is indicative of the effectiveness of the treatment of the disease or condition. The gene or genes (along with exemplary variances) are specified herein, in Tables 1-6, 12-17, and 18-23. Preferably the at least one variance includes a plurality of variances which may provide a haplotype or haplotypes. Preferably the joint presence of the plurality of variances is indicative of the potential effectiveness or safety of the treatment in a patient having such plurality of variances. The plurality of variances may each be indicative of the potential effectiveness of the treatment, and the effects of the individual variances may be independent or additive, or the plurality of variances may be indicative of the potential effectiveness if at least 2, 3, 4, or more appear jointly. The plurality of variances may also be combinations of these relationships. The plurality of variances may include variances from one, two, three or more gene loci.

In preferred embodiments of aspects of the invention involving genes relating to psychiatric or neurological disease or related conditions or the other diseases or conditions identified herein, or to pharmacological responses to compounds used to treat such diseases or conditions, the gene product is involved in a function as described in the Background of the Invention or otherwise described herein.

In some cases, the selection of a method of treatment, i.e., a therapeutic regimen, may incorporate selection of one or more from a plurality of medical therapies. Thus, the selection may be the selection of a method or methods which is/are more effective or less effective than certain other therapeutic regimens (with

either having varying safety parameters). Likewise or in combination with the preceding selection, the selection may be the selection of a method or methods, which is safer than certain other methods of treatment in the patient.

The selection may involve either positive selection or negative selection or both, meaning that the selection can involve a choice that a particular method would be an appropriate method to use and/or a choice that a particular method would be an inappropriate method to use. Thus, in certain embodiments, the presence of the at least one variance is indicative that the treatment will be effective or otherwise beneficial (or more likely to be beneficial) in the patient. Stating that the treatment will be effective means that the probability of beneficial therapeutic effect is greater than in a person not having the appropriate presence or absence of particular variances. In other embodiments, the presence of the at least one variance is indicative that the treatment will be ineffective or contra-indicated for the patient. For example, a treatment may be contra-indicated if the treatment results, or is more likely to result, in undesirable side effects, or an excessive level of undesirable side effects. A determination of what constitutes excessive side-effects will vary, for example, depending on the disease or condition being treated, the availability of alternatives, the expected or experienced efficacy of the treatment, and the tolerance of the patient. As for an effective treatment, this means that it is more likely that desired effect will result from the treatment administration in a patient with a particular variance or variances than in a patient who has a different variance or variances. Also in preferred embodiments, the presence of the at least one variance is indicative that the treatment is both effective and unlikely to result in undesirable effects or outcomes, or vice versa (is likely to have undesirable side effects but unlikely to produce desired therapeutic effects).

In reference to response to a treatment, the term "tolerance" refers to the ability of a patient to accept a treatment, based, e.g., on deleterious effects and/or effects on lifestyle. Frequently, the term principally concerns the patients perceived magnitude of deleterious effects such as nausea, weakness, dizziness, and diarrhea, among others. Such experienced effects can, for example, be due to general or cell-specific toxicity, activity on non-target cells, cross-reactivity on non-target cellular constituents (non-mechanism based), and/or side effects of activity on the target cellular constituents (mechanism based), or the cause of toxicity may not be understood. In any of these circumstances one may identify an association between the undesirable effects and variances in specific genes.

Adverse responses to drugs constitute a major medical problem, as shown in two recent meta-analyses (Lazarou, J. et al, Incidence of adverse drug reactions in hospitalized patients: a meta-analysis of prospective studies, JAMA 279:1200-1205,

1998; Bonn, Adverse drug reactions remain a major cause of death, Lancet 351:1183, 1998). An estimated 2.2 million hospitalized patients in the United States had serious adverse drug reactions in 1994, with an estimated 106,000 deaths (Lazarou et al.). To the extent that some of these adverse events are due to  
5 genetically encoded biochemical diversity among patients in pathways that effect drug action, the identification of variances that are predictive of such effects will allow for more effective and safer drug use.

In embodiments of this invention, the variance or variant form or forms of a gene is/are associated with a specific response to a drug. The frequency of a specific  
10 variance or variant form of the gene may correspond to the frequency of an efficacious response to administration of a drug. Alternatively, the frequency of a specific variance or variant form of the gene may correspond to the frequency of an adverse event resulting from administration of a drug. Alternatively the frequency of a specific variance or variant form of a gene may not correspond closely with the  
15 frequency of a beneficial or adverse response, yet the variance may still be useful for identifying a patient subset with high response or toxicity incidence because the variance may account for only a fraction of the patients with high response or toxicity. In such a case the preferred course of action is identification of a second or third or additional variances that permit identification of the patient groups not  
20 usefully identified by the first variance. Preferably, the drug will be effective in more than 20% of individuals with one or more specific variances or variant forms of the gene, more preferably in 40% and most preferably in >60%. In other embodiments, the drug will be toxic or create clinically unacceptable side effects in more than 10% of individuals with one or more variances or variant forms of the  
25 gene, more preferably in >30%, more preferably in >50%, and most preferably in >70% or in more than 90%.

Also in other embodiments, the method of selecting a treatment includes eliminating or excluding a treatment, where the presence or absence of the at least one variance is indicative that the treatment will be ineffective or contra-indicated,  
30 e.g., would result in excessive weight gain. In other preferred embodiments, in cases in which undesirable side-effects may occur or are expected to occur from a particular therapeutic treatment, the selection of a method of treatment can include identifying both a first and second treatment, where the first treatment is effective to treat the disease or condition, and the second treatment reduces a deleterious effect  
35 or enhance efficacy of the first treatment.

The phrase "eliminating a treatment" (similarly for excluding a treatment) refers to removing a possible treatment from consideration, e.g., for use with a particular patient based on the presence or absence of a particular variance(s) in one

or more genes in cells of that patient, or to stopping the administration of a treatment.

Usually, the treatment will involve the administration of a compound preferentially active or safe in patients with a form or forms of a gene, where the gene is one identified herein. The administration may involve a combination of compounds. Thus, in preferred embodiments, the method involves identifying such an active compound or combination of compounds, where the compound is less active or is less safe or both when administered to a patient having a different form of the gene.

Also in preferred embodiments, the method of selecting a treatment involves selecting a method of administration of a compound, combination of compounds, or pharmaceutical composition, for example, selecting a suitable dosage level and/or frequency of administration, and/or mode of administration of a compound. The method of administration can be selected to provide better, preferably maximum therapeutic benefit. In this context, "maximum" refers to an approximate local maximum based on the parameters being considered, not an absolute maximum.

Also in this context, a "suitable dosage level" refers to a dosage level which provides a therapeutically reasonable balance between pharmacological effectiveness and deleterious effects. Often this dosage level is related to the peak or average serum levels resulting from administration of a drug at the particular dosage level.

Similarly, a "frequency of administration" refers to how often in a specified time period a treatment is administered, e.g., once, twice, or three times per day, every other day, once per week, etc. For a drug or drugs, the frequency of administration is generally selected to achieve a pharmacologically effective average or peak serum level without excessive deleterious effects (and preferably while still being able to have reasonable patient compliance for self-administered drugs). Thus, it is desirable to maintain the serum level of the drug within a therapeutic window of concentrations for the greatest percentage of time possible without such deleterious effects as would cause a prudent physician to reduce the frequency of administration for a particular dosage level.

A particular gene or genes can be relevant to the treatment of more than one disease or condition, for example, the gene or genes can have a role in the initiation, development, course, treatment, treatment outcomes, or health-related quality of life outcomes of a number of different diseases, disorders, or conditions. Thus, in preferred embodiments, the disease or condition or treatment of the disease or condition is any which involves a gene from the gene list described herein as Tables 1-6, 12-17, and 18-23.

Determining the presence of a particular variance or plurality of variances in a particular gene in a patient can be performed in a variety of ways. In preferred embodiments, the detection of the presence or absence of at least one variance involves amplifying a segment of nucleic acid including at least one of the at least one variances. Preferably a segment of nucleic acid to be amplified is 500 nucleotides or less in length, more preferably 100 nucleotides or less, and most preferably 45 nucleotides or less. Also, preferably the amplified segment or segments includes a plurality of variances, or a plurality of segments of a gene or of a plurality of genes. In other embodiments, e.g., where a haplotype is to be determined, the segment of nucleic acid is at least 500 nucleotides in length, or at least 2 kb in length, or at least 5 kb in length.

In preferred embodiments, determining the presence of a set of variances in a specific gene related to treatment of disease, disorders, or dysfunctions or other related genes, or genes listed in Tables 1-6, 12-17, and 18-23, includes a haplotyping test that requires allele specific amplification of a large DNA segment of no greater than 25,000 nucleotides, preferably no greater than 10,000 nucleotides and most preferably no greater than 5,000 nucleotides. Alternatively one allele may be enriched by methods other than amplification prior to determining genotypes at specific variant positions on the enriched allele as a way of determining haplotypes. Preferably the determination of the presence or absence of a haplotype involves determining the sequence of the variant sites by methods such as chain terminating DNA sequencing or minisequencing, or by oligonucleotide hybridization or by mass spectrometry. For the use of mass spectrometry, the method can involve detection of the mass of a fragment or fragments and can further involve inferring the genotype (e.g., the specific variance at a site) from the masses determined.

The term "genotype" in the context of this invention refers to the alleles present in DNA from a subject or patient, where an allele can be defined by the particular nucleotide(s) present in a nucleic acid sequence at a particular site(s). Often a genotype is the nucleotide(s) present at a single polymorphic site known to vary in the human population.

In preferred embodiments, the detection of the presence or absence of the at least one variance involves contacting a nucleic acid sequence corresponding to one of the genes identified above or a product of such a gene with a probe. The probe is able to distinguish a particular form of the gene or gene product or the presence or a particular variance or variances, e.g., by differential binding or hybridization. Thus, exemplary probes include nucleic acid hybridization probes, peptide nucleic acid probes, nucleotide-containing probes which also contain at least one nucleotide analog, and antibodies, e.g., monoclonal antibodies, and other probes as discussed

herein. Those skilled in the art are familiar with the preparation of probes with particular specificities. Those skilled in the art will recognize that a variety of variables can be adjusted to optimize the discrimination between two variant forms of a gene, including changes in salt concentration, temperature, pH and addition of various compounds that affect the differential affinity of GC vs. AT base pairs, such as tetramethyl ammonium chloride. (See Current Protocols in Molecular Biology by F.M. Ausubel, R. Brent, R.E. Kingston, D.D. Moore, J.D. Seidman, K. Struhl, and V.B. Chanda (editors, John Wiley & Sons.)

In other preferred embodiments, determining the presence or absence of the at least one variance involves sequencing at least one nucleic acid sample. The sequencing involves sequencing of a portion or portions of a gene and/or portions of a plurality of genes which includes at least one variance site, and may include a plurality of such sites. Preferably, the portion is 500 nucleotides or less in length, more preferably 100 nucleotides or less, and most preferably 45 nucleotides or less in length. Such sequencing can be carried out by various methods recognized by those skilled in the art, including use of dideoxy termination methods (e.g., using dye-labeled dideoxy nucleotides) and the use of mass spectrometric methods. In addition, mass spectrometric methods may be used to determine the nucleotide present at a variance site. In preferred embodiments in which a plurality of variances is determined, the plurality of variances can constitute a haplotype or collection of haplotypes. Preferably the methods for determining genotypes or haplotypes are designed to be sensitive to all the common genotypes or haplotypes present in the population being studied (for example, a clinical trial population).

The terms "variant form of a gene", "form of a gene", or "allele" refer to one specific form of a gene in a population, the specific form differing from other forms of the same gene in the sequence of at least one, and frequently more than one, variant sites within the sequence of the gene. The sequences at these variant sites that differ between different alleles of the gene are termed "gene sequence variances" or "variances" or "variants". The term "alternative form" refers to an allele that can be distinguished from other alleles by having distinct variances at least one, and frequently more than one, variant sites within the gene sequence. Other terms known in the art to be equivalent include mutation and polymorphism, although mutation is often used to refer to an allele associated with a deleterious phenotype. In preferred aspects of this invention, the variances are selected from the group consisting of the variances listed in the variance tables herein or in a patent or patent application referenced and incorporated by reference in this disclosure. In the methods utilizing variance presence or absence, reference to the presence of a variance or variances means particular variances, i.e., particular nucleotides at

particular polymorphic sites, rather than just the presence of any variance in the gene.

Variances occur in the human genome at approximately one in every 500 – 1,000 bases within the human genome when two alleles are compared. When multiple alleles from unrelated individuals are compared the density of variant sites increases as different individuals, when compared to a reference sequence, will often have sequence variances at different sites. At most variant sites there are only two alternative nucleotides involving the substitution of one base for another or the insertion/deletion of one or more nucleotides. Within a gene there may be several variant sites. Variant forms of the gene or alternative alleles can be distinguished by the presence of alternative variances at a single variant site, or a combination of several different variances at different sites (haplotypes).

It is estimated that there are 3,300,000,000 bases in the sequence of a single haploid human genome. All human cells except germ cells are normally diploid. Each gene in the genome may span 100-10,000,000 bases of DNA sequence or 100-20,000 bases of mRNA. It is estimated that there are between 60,000 and 150,000 genes in the human genome. The "identification" of genetic variances or variant forms of a gene involves the discovery of variances that are present in a population. The identification of variances is required for development of a diagnostic test to determine whether a patient has a variant form of a gene that is known to be associated with a disease, condition, or predisposition or with the efficacy or safety of the drug. Identification of previously undiscovered genetic variances is distinct from the process of "determining" the status of known variances by a diagnostic test (often referred to as genotyping). The present invention provides exemplary variances in genes listed in the gene tables, as well as methods for discovering additional variances in those genes and a comprehensive written description of such additional possible variances. Also described are methods for DNA diagnostic tests to determine the DNA sequence at a particular variant site or sites.

The process of "identifying" or discovering new variances involves comparing the sequence of at least two alleles of a gene, more preferably at least 10 alleles and most preferably at least 50 alleles (keeping in mind that each somatic cell has two alleles). The analysis of large numbers of individuals to discover variances in the gene sequence between individuals in a population will result in detection of a greater fraction of all the variances in the population. Preferably the process of identifying reveals whether there is a variance within the gene; more preferably identifying reveals the location of the variance within the gene; more preferably identifying provides knowledge of the sequence of the nucleic acid sequence of the

variance, and most preferably identifying provides knowledge of the combination of different variances that comprise specific variant forms of the gene (referred to as alleles). In identifying new variances it is often useful to screen different population groups based on racial, ethnic, gender, and/or geographic origin because particular  
5 variances may differ in frequency between such groups. It may also be useful to screen DNA from individuals with a particular disease or condition of interest because they may have a higher frequency of certain variances than the general population.

The process of genotyping involves using diagnostic tests for specific  
10 variances that have already been identified. It will be apparent that such diagnostic tests can only be performed after variances and variant forms of the gene have been identified. Identification of new variances can be accomplished by a variety of methods, alone or in combination, including, for example, DNA sequencing, SSCP, heteroduplex analysis, denaturing gradient gel electrophoresis (DGGE),  
15 heteroduplex cleavage (either enzymatic as with T4 Endonuclease 7, or chemical as with osmium tetroxide and hydroxylamine), computational methods (described herein), and other methods described herein as well as others known to those skilled in the art. (See, for example: Cotton, R.G.H., Slowly but surely towards better scanning for mutations, Trends in Genetics 13(2): 43-6, 1997 or Current Protocols in  
20 Human Genetics by N.C. Dracoli, J.L. Haines, B.R. Korf, D.T. Moir, C.C. Morton, C.E. Seidman, D.R. Smith, and A. Boyle (editors), John Wiley & Sons.)

In the context of this invention, the term "analyzing a sequence" refers to determining at least some sequence information about the sequence, e.g., determining the nucleotides present at a particular site or sites in the sequence,  
25 particularly sites that are known to vary in a population, or determining the base sequence of all or of a portion of the particular sequence.

In the context of this invention, the term "haplotype" refers to a *cis* arrangement of two or more polymorphic nucleotides, i.e., variances, on a particular chromosome, e.g., in a particular gene. The haplotype preserves information about  
30 the phase of the polymorphic nucleotides – that is, which set of variances were inherited from one parent, and which from the other. A genotyping test does not provide information about phase. For example, an individual heterozygous at nucleotide 25 of a gene (both A and C are present) and also at nucleotide 100 (both G and T are present) could have haplotypes 25A – 100G and 25C – 100T, or  
35 alternatively 25A – 100T and 25C – 100G. Only a haplotyping test can discriminate these two cases definitively.

The terms "variances", "variants" and "polymorphisms", as used herein, may also refer to a set of variances, haplotypes or a mixture of the two, unless otherwise



indicated. Further, the term variance, variant or polymorphism (singular), as used herein, also encompasses a haplotype unless otherwise indicated. This usage is intended to minimize the need for cumbersome phrases such as: "...measure correlation between drug response and *a variance, variances, haplotype, haplotypes or a combination of variances and haplotypes...*", throughout the application.

Instead, the italicized text in the foregoing sentence can be represented by the word "variance", "variant" or "polymorphism". Similarly, the term genotype, as used herein, means a procedure for determining the status of one or more variances in a gene, including a set of variances comprising a haplotype. Thus phrases such as "...genotype a patient..." refer to determining the status of one or more variances, including a set of variances for which phase is known (i.e. a haplotype).

In preferred embodiments of this invention, the frequency of the variance or variant form of the gene in a population is known. Measures of frequency known in the art include "allele frequency", namely the fraction of genes in a population that have one specific variance or set of variances. The allele frequencies for any gene should sum to 1. Another measure of frequency known in the art is the "heterozygote frequency" namely, the fraction of individuals in a population who carry two alleles, or two forms of a particular variance or variant form of a gene, one inherited from each parent. Alternatively, the number of individuals who are homozygous for a particular form of a gene may be a useful measure. The relationship between allele frequency, heterozygote frequency, and homozygote frequency is described for many genes by the Hardy-Weinberg equation, which provides the relationship between allele frequency, heterozygote frequency and homozygote frequency in a freely breeding population at equilibrium. Most human variances are substantially in Hardy-Weinberg equilibrium. In a preferred aspect of this invention, the allele frequency, heterozygote frequency, and homozygote frequencies are determined experimentally. Preferably a variance has an allele frequency of at least 0.01, more preferably at least 0.05, still more preferably at least 0.10. However, the allele may have a frequency as low as 0.001 if the associated phenotype is, for example, a rare form of toxic reaction to a treatment or drug. Beneficial responses may also be rare.

In this regard, "population" refers to a defined group of individuals or a group of individuals with a particular disease or condition or individuals that may be treated with a specific drug identified by, but not limited to geographic, ethnic, race, gender, and/or cultural indices. In most cases a population will preferably encompass at least ten thousand, one hundred thousand, one million, ten million, or more individuals, with the larger numbers being more preferable. In preferred embodiments of this invention, the population refers to individuals with a specific

disease or condition that may be treated with a specific drug. In embodiments of this invention, the allele frequency, heterozygote frequency, or homozygote frequency of a specific variance or variant form of a gene is known. In preferred embodiments of this invention, the frequency of one or more variances that may predict response to a treatment is determined in one or more populations using a diagnostic test.

It should be emphasized that it is currently not generally practical to study an entire population to establish the association between a specific disease or condition or response to a treatment and a specific variance or variant form of a gene. Such studies are preferably performed in controlled clinical trials using a limited number of patients that are considered to be representative of the population with the disease. Since drug development programs are generally targeted at the largest possible population, the study population will generally consist of men and women, as well as members of various racial and ethnic groups, depending on where the clinical trial is being performed. This is important to establish the efficacy of the treatment in all segments of the population.

In the context of this invention, the term "probe" refers to a molecule that detectably distinguishes between target molecules differing in structure. Detection can be accomplished in a variety of different ways depending on the type of probe used and the type of target molecule. Thus, for example, detection may be based on discrimination of activity levels of the target molecule, but preferably is based on detection of specific binding. Examples of such specific binding include antibody binding and nucleic acid probe hybridization. Thus, for example, probes can include enzyme substrates, antibodies and antibody fragments, and nucleic acid hybridization probes. Thus, in preferred embodiments, the detection of the presence or absence of the at least one variance involves contacting a nucleic acid sequence which includes a variance site with a probe, preferably a nucleic acid probe, where the probe preferentially hybridizes with a form of the nucleic acid sequence containing a complementary base at the variance site as compared to hybridization to a form of the nucleic acid sequence having a non-complementary base at the variance site, where the hybridization is carried out under selective hybridization conditions. Such a nucleic acid hybridization probe may span two or more variance sites. Unless otherwise specified, a nucleic acid probe can include one or more nucleic acid analogs, labels or other substituents or moieties so long as the base-pairing function is retained.

As is generally understood, administration of a particular treatment, e.g., administration of a therapeutic compound or combination of compounds, is chosen depending on the disease or condition that is to be treated. Thus, in certain preferred

embodiments, the disease or condition is one for which administration of a treatment is expected to provide a therapeutic benefit; in certain embodiments, the compound is a compound identified herein, e.g., in a drug table (Tables 24-68).

As used herein, the terms "effective" and "effectiveness" includes both pharmacological effectiveness and physiological safety. Pharmacological effectiveness refers to the ability of the treatment to result in a desired biological effect in the patient. Physiological safety refers to the level of toxicity, or other adverse physiological effects at the cellular, organ and/or organism level (often referred to as side-effects) resulting from administration of the treatment. On the other hand, the term "ineffective" indicates that a treatment does not provide sufficient pharmacological effect to be therapeutically useful, even in the absence of deleterious effects, at least in the unstratified population. (Such a treatment may be ineffective in a subgroup that can be identified by the presence of one or more sequence variances or alleles.) "Less effective" means that the treatment results in a therapeutically significant lower level of pharmacological effectiveness and/or a therapeutically greater level of adverse physiological effects, e.g., greater liver toxicity.

Thus, in connection with the administration of a drug, a drug which is "effective against" a disease or condition indicates that administration in a clinically appropriate manner results in a beneficial effect for at least a statistically significant fraction of patients, such as a improvement of symptoms, a cure, a reduction in disease load, reduction in tumor mass or cell numbers, extension of life, improvement in quality of life, or other effect generally recognized as positive by medical doctors familiar with treating the particular type of disease or condition.

Effectiveness is measured in a particular population. In conventional drug development the population is generally every subject who meets the enrollment criteria (i.e. has the particular form of the disease or condition being treated). It is an aspect of the present invention that segmentation of a study population by genetic criteria can provide the basis for identifying a subpopulation in which a drug is effective against the disease or condition being treated.

The term "deleterious effects" refers to physical effects in a patient caused by administration of a treatment which are regarded as medically undesirable. Thus, for example, deleterious effects can include a wide spectrum of toxic effects injurious to health such as death of normally functioning cells when only death of diseased cells is desired, nausea, fever, inability to retain food, dehydration, damage to critical organs such as arrhythmias, renal tubular necrosis, fatty liver, or pulmonary fibrosis leading to coronary, renal, hepatic, or pulmonary insufficiency among many others. In this regard, the term "contra-indicated" means that a treatment results in

deleterious effects such that a prudent medical doctor treating such a patient would regard the treatment as unsuitable for administration. Major factors in such a determination can include, for example, availability and relative advantages of alternative treatments, consequences of non-treatment, and permanency of deleterious effects of the treatment.

It is recognized that many treatment methods, e.g., administration of certain compounds or combinations of compounds, may produce side-effects or other deleterious effects in patients. Such effects can limit or even preclude use of the treatment method in particular patients, or may even result in irreversible injury, dysfunction, or death of the patient. Thus, in certain embodiments, the variance information is used to select both a first method of treatment and a second method of treatment. Usually the first treatment is a primary treatment which provides a physiological effect directed against the disease or condition or its symptoms. The second method is directed to reducing or eliminating one or more deleterious effects or enhancing efficacy of the first treatment, e.g., to reduce a general toxicity or to reduce a side effect of the primary treatment. Thus, for example, the second method can be used to allow use of a greater dose or duration of the first treatment, or to allow use of the first treatment in patients for whom the first treatment would not be tolerated or would be contra-indicated in the absence of a second method to reduce deleterious effects or to potentiate the effectiveness of the first treatment.

In a related aspect, the invention concerns a method for providing a correlation between a patient genotype and effectiveness of a treatment, by determining the presence or absence of a particular known variance or variances in cells of a patient for a gene from Tables 1-6, 12-17, and 18-23, or other gene related to neurological disease or other disease identified herein, and providing a result indicating the expected effectiveness of a treatment for a disease or condition. The result may be formulated by comparing the genotype of the patient with a list of variances indicative of the effectiveness of a treatment, e.g., administration of a drug described herein. The determination may be by methods as described herein or other methods known to those skilled in the art.

In a related aspect, the invention provides a method for selecting a method of treatment for a patient suffering from a disease or condition as identified herein by comparing at least one variance in at least one gene in the patient, with a list of variances in the gene from Tables 1-6, 12-17, and 18-23, or other gene related to a disease or condition listed herein, which are indicative of the effectiveness of at least one method of treatment. Preferably the comparison involves a plurality of variances or a haplotype indicative of the effectiveness of at least one method of treatment. Also, preferably the list of variances includes a plurality of variances.

Similar to the above aspect, in preferred embodiments the at least one method of treatment involves the administration of a compound effective in at least some patients with a disease or condition; the presence or absence of the at least one variance is indicative that the treatment will be effective in the patient; and/or the presence or absence of the at least one variance is indicative that the treatment will be ineffective or contra-indicated in the patient; and/or the treatment is a first treatment and the presence or absence of the at least one variance is indicative that a second treatment will be beneficial to reduce a deleterious effect of or potentiate the effectiveness of the first treatment; and/or the at least one treatment is a plurality of methods of treatment. For a plurality of treatments, preferably the selecting involves determining whether any of the methods of treatment will be more effective than at least one other of the plurality of methods of treatment. Yet other embodiments are provided as described for the preceding aspect in connection with methods of treatment using administration of a compound; treatment of various diseases, and variances in particular genes.

In the context of variance information in the methods of this invention, the term "list" refers to one or more, preferably at least 2, 3, 4, 5, 7, or 10 variances that have been identified for a gene of potential importance in accounting for inter-individual variation in treatment response. Preferably there is a plurality of variances for the gene, preferably a plurality of variances for the particular gene. Preferably, the list is recorded in written or electronic form. For example, identified variances of identified genes are recorded for some of the genes in Tables 12-17 and 18-23; additional variances for genes in Tables 1-6 can be readily identified by one skilled in the art using any of a variety of methods. The list may also contain haplotypes, either alone or with other variances.

In addition to the basic method of treatment, often the mode of administration of a given compound as a treatment for a disease or condition in a patient is significant in determining the course and/or outcome of the treatment for the patient. Thus, the invention also provides a method for selecting a method of administration of a compound to a patient suffering from a disease or condition, by determining the presence or absence of at least one variance in cells of the patient in at least one identified gene from Tables 1-6, 12-17, and 18-23, where such presence or absence is indicative of an appropriate method of administration of the compound. Preferably, the selection of a method of treatment (a treatment regimen) involves selecting a dosage level or frequency of administration or route of administration of the compound or combinations of those parameters. In preferred embodiments, two or more compounds are to be administered, and the selecting involves selecting a method of administration for one, two, or more than two of the

compounds, jointly, concurrently, or separately. As understood by those skilled in the art, such plurality of compounds may be used in combination therapy, and thus may be formulated in a single drug, or may be separate drugs administered concurrently, serially, or separately. Other embodiments are as indicated above for selection of second treatment methods, methods of identifying variances, and methods of treatment as described for aspects above.

In another aspect, the invention provides a method for selecting a patient for administration of a method of treatment for a disease or condition, or of selecting a patient for a method of administration of a treatment, by comparing the presence or absence of at least one variance in a gene as identified above in cells of a patient, with a list of variances in the gene, where the presence or absence of the at least one variance is indicative that the treatment or method of administration will be effective in the patient. If the at least one variance is present in the patient's cells, then the patient is selected for administration of the treatment.

In preferred embodiments, the disease or the method of treatment is as described in aspects above, specifically including, for example, those described for selecting a method of treatment.

In another aspect, the invention provides a method for identifying a subset of patients with enhanced or diminished response or tolerance to a treatment method or a method of administration of a treatment where the treatment is for a disease or condition in the patient. The method involves correlating one or more variances in one or more genes as identified in aspects above in a plurality of patients with response to a treatment or a method of administration of a treatment. The correlation may be performed by determining the one or more variances in the one or more genes in the plurality of patients and correlating the presence or absence of each of the variances (alone or in various combinations) with the patient's response to treatment. The variances may be previously known to exist or may also be determined in the present method or combinations of prior information and newly determined information may be used. The enhanced or diminished response should be statistically significant, preferably such that  $p = 0.10$  or less, more preferably  $0.05$  or less, and most preferably  $0.02$  or less. A positive correlation between the presence of one or more variances and an enhanced response to treatment is indicative that the treatment is particularly effective in the group of patients having those variances. A positive correlation of the presence of the one or more variances with a diminished response to the treatment is indicative that the treatment will be less effective in the group of patients having those variances. Such information is useful, for example, for selecting or de-selecting patients for a particular treatment or method of administration of a treatment, or for demonstrating that a group of

patients exists for which the treatment or method of treatment would be particularly beneficial or contra-indicated. Such demonstration can be beneficial, for example, for obtaining government regulatory approval for a new drug or a new use of a drug

5 In preferred embodiments, the variances are in at least one of the identified genes listed on Tables 1-6, 12-17, and 18-23, or are particular variances described herein. Also, preferred embodiments include drugs, treatments, variance identification or determination, determination of effectiveness, and/or diseases as described for aspects above or otherwise described herein.

10 In preferred embodiments, the correlation of patient responses to therapy according to patient genotype is carried out in a clinical trial, e.g., as described herein according to any of the variations described. Detailed description of methods for associating variances with clinical outcomes using clinical trials are provided below. Further, in preferred embodiments the correlation of pharmacological effect (positive or negative) to treatment response according to genotype or haplotype in  
15 such a clinical trial is part of a regulatory submission to a government agency leading to approval of the drug. Most preferably the compound or compounds would not be approvable in the absence of the genetic information allowing identification of an optimal responder population.

20 As indicated above, in aspects of this invention involving selection of a patient for a treatment, selection of a method or mode of administration of a treatment, and selection of a patient for a treatment or a method of treatment, the selection may be positive selection or negative selection. Thus, the methods can include eliminating or excluding a treatment for a patient, eliminating or excluding a method or mode of administration of a treatment to a patient, or elimination or  
25 exclusion of a patient for a treatment or method of treatment.

Also, in methods involving identification and/or comparison of variances present in a gene of a patient, the methods can involve such identification or comparison for a plurality of genes. Preferably, the genes are functionally related to the same disease or condition, or to the aspect of disease pathophysiology that is  
30 being subjected to pharmacological manipulation by the treatment (e.g., a drug), or to the activation or inactivation or elimination of the drug, and more preferably the genes are involved in the same biochemical process or pathway.

35 In another aspect, the invention provides a method for identifying the forms of a gene in an individual, where the gene is one specified as for aspects above, by determining the presence or absence of at least one variance in the gene. In preferred embodiments, the at least one variance includes at least one variance selected from the group of variances identified in variance tables herein. Preferably, the presence or absence of the at least one variance is indicative of the effectiveness

of a therapeutic treatment in a patient suffering from a disease or condition and having cells containing the at least one variance.

The presence or absence of the variances can be determined in any of a variety of ways as recognized by those skilled in the art. For example, the  
5 nucleotide sequence of at least one nucleic acid sequence which includes at least one variance site (or a complementary sequence) can be determined, such as by chain termination methods, hybridization methods or by mass spectrometric methods. Likewise, in preferred embodiments, the determining involves contacting a nucleic acid sequence or a gene product of one of one of the genes with a probe that  
10 specifically identifies the presence or absence of a form of the gene. For example, a probe, e.g., a nucleic acid probe, can be used which specifically binds, e.g., hybridizes, to a nucleic acid sequence corresponding to a portion of the gene and which includes at least one variance site under selective binding conditions. As described for other aspects, determining the presence or absence of at least two  
15 variances and their relationship on the two gene copies present in a patient can constitute determining a haplotype or haplotypes.

Other preferred embodiments involve variances related to types of treatment, drug responses, diseases, nucleic acid sequences, and other items related to variances and variance determination as described for aspects above.

20 In yet another aspect, the invention provides a pharmaceutical composition which includes a compound which has a differential effect in patients having at least one copy, or alternatively, two copies of a form of a gene as identified for aspects above and a pharmaceutically acceptable carrier, excipient, or diluent. The composition is adapted to be preferentially effective to treat a patient with cells  
25 containing the one, two, or more copies of the form of the gene.

In preferred embodiments of aspects involving pharmaceutical compositions, active compounds, or drugs, the material is subject to a regulatory limitation or restriction on approved uses or indications, e.g., by the U.S. Food and Drug Administration (FDA), limiting approved use of the composition to patients having  
30 at least one copy of the particular form of the gene which contains at least one variance. Alternatively, the composition is subject to a regulatory limitation or restriction on approved uses indicating that the composition is not approved for use or should not be used in patients having at least one copy of a form of the gene including at least one variance. Also in preferred embodiments, the composition is  
35 packaged, and the packaging includes a label or insert indicating or suggesting beneficial therapeutic approved use of the composition in patients having one or two copies of a form of the gene including at least one variance. Alternatively, the label or insert limits approved use of the composition to patients having zero or one



or two copies of a form of the gene including at least one variance. The latter embodiment would be likely where the presence of the at least one variance in one or two copies in cells of a patient means that the composition would be ineffective or deleterious to the patient. Also in preferred embodiments, the composition is indicated for use in treatment of a disease or condition which is one of those identified for aspects above. Also in preferred embodiments, the at least one variance includes at least one variance from those identified herein.

The term "packaged" means that the drug, compound, or composition is prepared in a manner suitable for distribution or shipping with a box, vial, pouch, bubble pack, or other protective container, which may also be used in combination. The packaging may have printing on it and/or printed material may be included in the packaging.

In preferred embodiments, the drug is selected from the drug classes or specific exemplary drugs identified in an example, in a table herein, and is subject to a regulatory limitation or suggestion or warning as described above that limits or suggests limiting approved use to patients having specific variances or variant forms of a gene identified in Examples or in the gene list provided below in order to achieve maximal benefit and avoid toxicity or other deleterious effect.

A pharmaceutical composition can be adapted to be preferentially effective in a variety of ways. In some cases, an active compound is selected which was not previously known to be differentially active, or which was not previously recognized as a potential therapeutic compound. In some cases, the concentration of an active compound which has differential activity can be adjusted such that the composition is appropriate for administration to a patient with the specified variances. For example, the presence of a specified variance may allow or require the administration of a much larger dose, which would not be practical with a previously utilized composition. Conversely, a patient may require a much lower dose, such that administration of such a dose with a prior composition would be impractical or inaccurate. Thus, the composition may be prepared in a higher or lower unit dose form, or prepared in a higher or lower concentration of the active compound or compounds. In yet other cases, the composition can include additional compounds needed to enable administration of a particular active compound in a patient with the specified variances, which was not in previous compositions, e.g., because the majority of patients did not require or benefit from the added component.

The term "differential" or "differentially" generally refers to a statistically significant different level in the specified property or effect. Preferably, the difference is also functionally significant. Thus, "differential binding or hybridization" is sufficient difference in binding or hybridization to allow

discrimination using an appropriate detection technique. Likewise, "differential effect" or "differentially active" in connection with a therapeutic treatment or drug refers to a difference in the level of the effect or activity which is distinguishable using relevant parameters and techniques for measuring the effect or activity being considered. Preferably the difference in effect or activity is also sufficient to be clinically significant, such that a corresponding difference in the course of treatment or treatment outcome would be expected, at least on a statistical basis.

Also usefully provided in the present invention are probes which specifically recognize a nucleic acid sequence corresponding to a variance or variances in a gene as identified in aspects above or a product expressed from the gene, and are able to distinguish a variant form of the sequence or gene or gene product from one or more other variant forms of that sequence, gene, or gene product under selective conditions. Those skilled in the art recognize and understand the identification or determination of selective conditions for particular probes or types of probes. An exemplary type of probe is a nucleic acid hybridization probe, which will selectively bind under selective binding conditions to a nucleic acid sequence or a gene product corresponding to one of the genes identified for aspects above. Another type of probe is a peptide or protein, e.g., an antibody or antibody fragment which specifically or preferentially binds to a polypeptide expressed from a particular form of a gene as characterized by the presence or absence of at least one variance. Thus, in another aspect, the invention concerns such probes. In the context of this invention, a "probe" is a molecule, commonly a nucleic acid, though also potentially a protein, carbohydrate, polymer, or small molecule, that is capable of binding to one variance or variant form of the gene to a greater extent than to a form of the gene having a different base at one or more variance sites, such that the presence of the variance or variant form of the gene can be determined. Preferably the probe distinguishes at least one variance identified in Examples, tables or lists below or is a variance otherwise identified in a gene identified herein.

In preferred embodiments, the probe is a nucleic acid probe at least 15, preferably at least 17 nucleotides in length, more preferably at least 20 or 22 or 25, preferably 500 or fewer nucleotides in length, more preferably 200 or 100 or fewer, still more preferably 50 or fewer, and most preferably 30 or fewer. In preferred embodiments, the probe has a length in a range between from any one of the above lengths to any other of the above lengths (including endpoints). In the case of certain types of probes, e.g., peptide nucleic acid probes, the probe may be shorter, e.g., 6, 7, 8, 10, or 12 nucleotides in length. The probe specifically hybridizes under selective hybridization conditions to a nucleic acid sequence corresponding to a portion of one of the genes identified in connection with above aspects. The nucleic

acid sequence includes at least one variance site. Also in preferred embodiments, the probe has a detectable label, preferably a fluorescent label. A variety of other detectable labels are known to those skilled in the art. Such a nucleic acid probe can also include one or more nucleic acid analogs.

5 In preferred embodiments, the probe is an antibody or antibody fragment which specifically binds to a gene product expressed from a form of one of the above genes, where the form of the gene has at least one specific variance with a particular base at the variance site, and preferably a plurality of such variances.

10 In connection with nucleic acid probe hybridization, the term "specifically hybridizes" indicates that the probe hybridizes to a sufficiently greater degree to the target sequence than to a sequence having a mismatched base at least one variance site to allow distinguishing such hybridization. The term "specifically hybridizes" thus means that the probe hybridizes to the target sequence, and not to non-target sequences, at a level which allows ready identification of probe/target sequence  
15 hybridization under selective hybridization conditions. Thus, "selective hybridization conditions" refer to conditions which allow such differential binding. Similarly, the terms "specifically binds" and "selective binding conditions" refer to such differential binding of any type of probe, e.g., antibody probes, and to the conditions which allow such differential binding. Typically hybridization reactions  
20 to determine the status of variant sites in patient samples are carried out with two different probes, one specific for each of the (usually two) possible variant nucleotides. The complementary information derived from the two separate hybridization reactions is useful in corroborating the results.

25 Likewise, the invention provides an isolated, purified or enriched nucleic acid sequence of 15 to 500 nucleotides in length, preferably 15 to 100 nucleotides in length, more preferably 15 to 50 nucleotides in length, and most preferably 15 to 30 nucleotides in length, which has a sequence which corresponds to a portion of one of the genes identified for aspects above. Preferably the lower limit for the preceding ranges is 17, 20, 22, or 25 nucleotides in length. In other embodiments, the nucleic  
30 acid sequence is 30 to 300 nucleotides in length, or 45 to 200 nucleotides in length, or 45 to 100 nucleotides in length. The nucleic acid sequence includes at least one variance site. Such sequences can, for example, be amplification products of a sequence which spans or includes a variance site in a gene identified herein. Likewise, such a sequence can be a primer that is able to bind to or extend through a  
35 variance site in such a gene. Yet another example is a nucleic acid hybridization probe comprised of such a sequence. In such probes, primers, and amplification products, the nucleotide sequence can contain a sequence or site corresponding to a variance site or sites, for example, a variance site identified herein. Preferably the

presence or absence of a particular variant form in the heterozygous or homozygous state is indicative of the effectiveness of a method of treatment in a patient.

In reference to nucleic acid sequences which "correspond" to a gene, the term "correspond" refers to a nucleotide sequence relationship, such that the  
5 nucleotide sequence has a nucleotide sequence which is the same as the reference gene or an indicated portion thereof, or has a nucleotide sequence which is exactly complementary in normal Watson-Crick base pairing, or is an RNA equivalent of such a sequence, e.g., an mRNA, or is a cDNA derived from an mRNA of the gene.

In another aspect, the invention provides a method for determining a  
10 genotype of an individual in relation to one or more variances in one or more of the genes identified in above aspects by using mass spectrometric determination of a nucleic acid sequence which is a portion of a gene identified for other aspects of this invention or a complementary sequence. Such mass spectrometric methods are known to those skilled in the art. In preferred embodiments, the method involves  
15 determining the presence or absence of a variance in a gene; determining the nucleotide sequence of the nucleic acid sequence; the nucleotide sequence is 100 nucleotides or less in length, preferably 50 or less, more preferably 30 or less, and still more preferably 20 nucleotides or less. In general, such a nucleotide sequence includes at least one variance site, preferably a variance site which is informative  
20 with respect to the expected response of a patient to a treatment as described for above aspects.

As indicated above, many therapeutic compounds or combinations of compounds or pharmaceutical compositions show variable efficacy and/or safety in various patients in whom the compound or compounds is administered. Thus, it is  
25 beneficial to identify variances in relevant genes, e.g., genes related to the action or toxicity of the compound or compounds. Thus, in a further aspect, the invention provides a method for determining whether a compound has a differential effect due to the presence or absence of at least one variance in a gene or a variant form of a gene, where the gene is a gene identified for aspects above.

The method involves identifying a first patient or set of patients suffering  
30 from a disease or condition whose response to a treatment differs from the response (to the same treatment) of a second patient or set of patients suffering from the same disease or condition, and then determining whether the occurrence or frequency of occurrence of at least one variance in at least one gene differs between the first  
35 patient or set of patients and the second patient or set of patients. A correlation or other appropriate statistical test between the presence or absence of the variance or variances and the response of the patient or patients to the treatment indicates that the variance provides information about variable patient response. In general, the

method will involve identifying at least one variance in at least one gene. An alternative approach is to identify a first patient or set of patients suffering from a disease or condition and having a particular genotype, haplotype or combination of genotypes or haplotypes, and a second patient or set of patients suffering from the same disease or condition that have a genotype or haplotype or sets of genotypes or haplotypes that differ in a specific way from those of the first set of patients.

Subsequently the extent and magnitude of clinical response can be compared between the first patient or set of patients and the second patient or set of patients. A correlation between the presence or absence of a variance or variances or haplotypes and the response of the patient or patients to the treatment indicates that the variance provides information about variable patient response and is useful for the present invention.

The method can utilize a variety of different informative comparisons to identify correlations. For example a plurality of pairwise comparisons of treatment response and the presence or absence of at least one variance can be performed for a plurality of patients. Likewise, the method can involve comparing the response of at least one patient homozygous for at least one variance with at least one patient homozygous for the alternative form of that variance or variances. The method can also involve comparing the response of at least one patient heterozygous for at least one variance with the response of at least one patient homozygous for the at least one variance. Preferably the heterozygous patient response is compared to both alternative homozygous forms, or the response of heterozygous patients is grouped with the response of one class of homozygous patients and said group is compared to the response of the alternative homozygous group.

Such methods can utilize either retrospective or prospective information concerning treatment response variability. Thus, in a preferred embodiment, it is previously known that patient response to the method of treatment is variable.

Also in preferred embodiments, the disease or condition is as for other aspects of this invention; for example, the treatment involves administration of a compound or pharmaceutical composition.

In preferred embodiments, the method involves a clinical trial, e.g., as described herein. Such a trial can be arranged, for example, in any of the ways described herein, e.g., in the Detailed Description.

The present invention also provides methods of treatment of a disease or condition as identified herein. Such methods combine identification of the presence or absence of particular variances, preferably in a gene or genes from Tables 1-6, 12-17, and 18-23, with the administration of a compound; identification of the presence of particular variances with selection of a method of treatment and

administration of the treatment; and identification of the presence or absence of particular variances with elimination of a method of treatment based on the variance information indicating that the treatment is likely to be ineffective or contra-indicated, and thus selecting and administering an alternative treatment effective  
5 against the disease or condition. Thus, preferred embodiments of these methods incorporate preferred embodiments of such methods as described for such sub-aspects.

As used herein, a "gene" is a sequence of DNA present in a cell that directs the expression of a "biologically active" molecule or "gene product", most  
10 commonly by transcription to produce RNA and translation to produce protein. The "gene product" is most commonly a RNA molecule or protein or a RNA or protein that is subsequently modified by reacting with, or combining with, other constituents of the cell. Such modifications may include, without limitation, modification of proteins to form glycoproteins, lipoproteins, and phosphoproteins, or other  
15 modifications known in the art. RNA may be modified without limitation by polyadenylation, splicing, capping or export from the nucleus or by covalent or noncovalent interactions with proteins. The term "gene product" refers to any product directly resulting from transcription of a gene. In particular this includes partial, precursor, and mature transcription products (i.e., pre-mRNA and mRNA),  
20 and translation products with or without further processing including, without limitation, lipidation, phosphorylation, glycosylation, or combinations of such processing

The term "gene involved in the origin or pathogenesis of a disease or condition" refers to a gene that harbors mutations or polymorphisms that contribute  
25 to the cause of disease, or variances that affect the progression of the disease or expression of specific characteristics of the disease. The term also applies to genes involved in the synthesis, accumulation, or elimination of products that are involved in the origin or pathogenesis of a disease or condition including, without limitation, proteins, lipids, carbohydrates, hormones, or small molecules.

The term "gene involved in the action of a drug" refers to any gene whose gene product affects the efficacy or safety of the drug or affects the disease process being treated by the drug, and includes, without limitation, genes that encode gene products that are targets for drug action, gene products that are involved in the metabolism, activation or degradation of the drug, gene products that are involved in  
35 the bioavailability or elimination of the drug to the target, gene products that affect biological pathways that, in turn, affect the action of the drug such as the synthesis or degradation of competitive substrates or allosteric effectors or rate-limiting reaction, or, alternatively, gene products that affect the pathophysiology of the

disease process via pathways related or unrelated to those altered by the presence of the drug compound. (Particular variances in the latter category of genes may be associated with patient groups in whom disease etiology is more or less susceptible to amelioration by the drug. The "action" of a drug refers to its effect on biological products within the body. The action of a drug also refers to its effects on the signs or symptoms of a disease or condition, or effects of the drug that are unrelated to the disease or condition leading to unanticipated effects on other processes. Such unanticipated processes often lead to adverse events or toxic effects. The terms "adverse event" or "toxic" event" are known in the art and include, without limitation, those listed in the FDA reference system for adverse events.

In accordance with the aspects above and the Detailed Description below, there is also described for this invention an approach for developing drugs that are explicitly indicated for, and/or for which approved use is restricted to or recommended to be restricted to individuals in the population with specific variances or combinations of variances, as determined by diagnostic tests for variances or variant forms of certain genes involved in the disease or condition or involved in the action or metabolism or transport of the drug. Such drugs may provide more effective treatment for a disease or condition in a population identified or characterized with the use of a diagnostic test for a specific variance or variant form of the gene if the gene is involved in the action of the drug or in determining a characteristic of the disease or condition. Such drugs may be developed using the diagnostic tests for specific variances or variant forms of a gene to determine the inclusion of patients in a clinical trial.

Thus, the invention also provides a method for producing a pharmaceutical composition by identifying a compound which has differential activity or effectiveness against a disease or condition in patients having at least one variance in a gene, preferably in a gene from Tables 1-6, compounding the pharmaceutical composition by combining the compound with a pharmaceutically acceptable carrier, excipient, or diluent such that the composition is preferentially effective in patients who have at least one copy of the variance or variances. In some cases, the patient has two copies of the variance or variances. In preferred embodiments, the disease or condition, gene or genes, variances, methods of administration, or method of determining the presence or absence of variances is as described for other aspects of this invention. In preferred embodiments, the active component of the pharmaceutical composition is a compound listed in the compound tables below (Tables 24 through 68), or a compound chemically related to one of the listed compounds.

Similarly, the invention provides a method for producing a pharmaceutical agent by identifying a compound which has differential activity against a disease or condition in patients having at least one copy of a form of a gene, preferably a gene from Tables 1 through 6, having at least one variance and synthesizing the compound in an amount sufficient to provide a pharmaceutical effect in a patient suffering from the disease or condition. The compound can be identified by conventional screening methods and its activity confirmed. For example, compound libraries can be screened to identify compounds which differentially bind to products of variant forms of a particular gene product, or which differentially affect expression of variant forms of the particular gene, or which differentially affect the activity of a product expressed from such gene. Alternatively, the design of a compound can exploit knowledge of the variances provided herein to avoid significant allele specific effects, in order to reduce the likelihood of significant pharmacogenetic effects during the clinical development process. Preferred embodiments are as for the preceding aspect.

In another aspect, the invention provides a method of treating a disease or condition in a patient by selecting a patient whose cells have an allele of an identified gene, preferably a gene selected from the genes listed in Tables 1 through 6. The allele contains at least one variance correlated with more effective response to a treatment of said disease or condition. The method also includes altering the level of activity in cells of the patient of a product of the allele, where the altering provides a therapeutic effect.

Preferably the allele contains a variance as shown in Tables 1-6, 12-17, and 18-23, or other variance table herein, or in Table 1 or 3 of Stanton et al., U.S. Application No. 09/300,747. Also preferably, the altering involves administering to the patient a compound preferentially active on at least one but less than all alleles of the gene.

Preferred embodiments include those as described above for other aspects of treating a disease or condition.

As recognized by those skilled in the art, all the methods of treating described herein include administration of the treatment to a patient.

In a further aspect, the invention provides a method for determining a treatment effective to treat a disease or condition by altering the level of activity of a product of an allele of a gene selected from the genes listed in Tables 1-6, and determining whether that alteration provides a differential effect (with respect to reducing or alleviating a disease or condition, or with respect to variation in toxicity or tolerance to a treatment) in patients with at least one copy of at least one allele of the gene as compared to patients with at least one copy of one alternative allele.,



The presence of such a differential effect indicates that altering the level or activity of the gene provides at least part of an effective treatment for the disease or condition.

Preferably the method for determining a treatment is carried out in a clinical trial, e.g., as described above and/or in the Detailed Description below.

In a further aspect, the invention provides a method for determining a treatment effective to treat a disease or condition by altering the level of activity of a product of an allele of a gene selected from the genes listed in Tables 1-6, and determining whether that alteration provides a differential effect (with respect to reducing or alleviating a disease or condition, or with respect to variation in toxicity or tolerance to a treatment) in patients with at least one copy of at least one allele of the gene as compared to patients with at least one copy of one alternative allele. The presence of such a differential effect indicates that altering the level or activity of the gene provides at least part of an effective treatment for the disease or condition.

Preferably the method for determining a method of treatment is carried out in a clinical trial, e.g., as described above and/or in the Detailed Description below.

In still another aspect, the invention provides a method for performing a clinical trial or study, which includes selecting or stratifying subjects in the trial or study using a variance or variances or haplotypes from one or more genes specified in Tables 1-6, 12-17, and 18-23. Preferably the differential efficacy, tolerance, or safety of a treatment in a subset of patients who have a particular variance, variances, or haplotype in a gene or genes from Tables 1-6, 12-17, and 18-23 is determined by conducting a clinical trial and using a statistical test to assess whether a relationship exists between efficacy, tolerance, or safety and the presence or absence of any of the variances or haplotype in one or more of the genes. Results of the clinical trial or study are indicative of whether a higher or lower efficacy, tolerance, or safety of the treatment in a subset of patients is associated with any of the variance or variances or haplotype in one or more of the genes. In preferred embodiments, the clinical trial or study is a Phase I, II, III, or IV trial or study. Preferred embodiments include the stratifications and/or statistical analyses as described below in the Detailed Description.

In preferred embodiments, normal subjects or patients are prospectively stratified by genotype in different genotype-defined groups, including the use of genotype as an enrollment criterion, using a variance, variances or haplotypes from

Tables 1-6, 12-17, and 18-23, and subsequently a biological or clinical response variable is compared between the different genotype-defined groups. In preferred embodiments, normal subjects or patients in a clinical trial or study are stratified by a biological or clinical response variable in different biologically or clinically-defined groups, and subsequently the frequency of a variance, variances or haplotypes from Tables 1-6, 12-17, and 18-23 is measured in the different biologically or clinically defined groups.

In preferred embodiments, e.g., of the above two analyses, the normal subjects or patients in a clinical trial or study are stratified by at least one demographic characteristic selected from the groups consisting of sex, age, racial origin, ethnic origin, or geographic origin.

Generally the method will involve assigning patients to a group to receive the method of treatment or to a control group.

In yet another aspect, the invention provides experimental methods for finding additional variances in a gene provided in Tables 1-6, 12-17, 18-23. A number of experimental methods can also beneficially be used to identify variances. Thus, the invention provides methods for producing cDNA (Example 1) and detecting additional variances in the genes provided in Tables 1-6, 12-17, 18-23, using the single strand conformation polymorphism (SSCP) method (Example 2), the T4 Endonuclease VII method (Example 3) or DNA sequencing (Example 4) or other methods pointed out below. The application of these methods to the identified genes will provide identification of additional variances that can affect inter-individual variation in drug or other treatment response. One skilled in the art will recognize that many methods for experimental variance detection have been described (in addition to the exemplary methods of examples 2, 3, 4) and can be utilized. These additional methods include chemical cleavage of mismatches (see, e.g., Ellis T.P., et al., Chemical cleavage of mismatch: a new look at an established method. *Human Mutation* 11(5):345-53, 1998), denaturing gradient gel electrophoresis (see, e.g., Van Orsouw N.J., et al., Design and application of 2-D DGGE-based gene mutational scanning tests. *Genet Anal.* 14(5-6):205-13, 1999) and heteroduplex analysis (see, e.g., Ganguly A., et al., Conformation-sensitive gel electrophoresis for rapid detection of single-base differences in double-stranded PCR products and DNA fragments: evidence for solvent-induced bends in DNA heteroduplexes. *Proc Natl Acad Sci U S A.* 90 (21):10325-9, 1993). Table 3 of Stanton et al., U.S. Application No. 09/300,747, provides a description of the additional possible variances that could be detected by one skilled in the art by

testing an identified gene in Tables 1-6, 12-17, 18-23, using the variance detection methods described or other methods which are known or are developed.

The present invention provides a method for treating a patient at risk for a disease, disorder, dysfunction or condition (for example to prevent or delay the onset of frank disease) or a patient already diagnosed with a said disease or a disease associated with said disease. The methods include identifying such a patient and determining the patient's genotype or haplotype for an identified gene or genes. The patient identification can, for example, be based on clinical evaluation using conventional clinical metrics and/or on evaluation of a genetic variance or variances in one or more genes, preferably a gene or genes from Tables 1-6. The invention provides a method for using the patient's genotype status to determine a treatment protocol that includes a prediction of the efficacy and/or safety of a therapy.

In another aspect, the invention provides a method for treating a patient at risk for a drug-induced disease, disorder or dysfunction by a) identifying a patient with such a risk, b) determining the genotypic allele status of the patient, and c) converting the data obtained in step b) into a treatment protocol that includes a comparison of the genotypic allele status determination with the allele frequency of a control population. This comparison allows for a statistical calculation of the patient's risk for having drug-induced disease, disorder, or dysfunction, e.g., based on correlation of the allele frequencies for a population with response or disease occurrence and/or severity. In preferred embodiments, the method provides a treatment protocol that predicts a patient being heterozygous or homozygous for an identified allele to exhibit signs and or symptoms of drug-induced disease, disorder, or dysfunction and a patient who is wild-type homozygous for the said allele, as responding favorably to these therapies.

In an another related aspect, the invention provides a method for identifying a patient for participation in a clinical trial of a therapy for the treatment of a disease or an associated pathological or psychiatric condition.

The method for identification of a subject of the participation in a clinical trial of a therapy for a disease described in this invention involves determining the genotype or haplotype of a patient with (or at risk for) a disease as identified herein. Preferably the genotype is for a variance in a gene from Tables 1-6. Patients with eligible genotypes are then assigned to a treatment or placebo group, preferably by a blinded randomization procedure. In preferred embodiments, the selected patients have at least no copies, one copy or two copies of a wild type specific allele of identified a gene or genes identified in Tables 1-6. Alternatively, patients selected for the clinical trial may have zero, one or two copies of an allele belonging to a set of alleles, where the set of alleles comprise a group of related alleles. One

procedure for rigorously defining a set of alleles is by applying phylogenetic methods to the analysis of haplotypes. (See, for example: Templeton A.R., Crandall K.A. and C.F. Sing, A cladistic analysis of phenotypic associations with haplotypes inferred from restriction endonuclease mapping and DNA sequence data. III.

5 Cladogram estimation. *Genetics* 1992 Oct. 132(2):619-33.) Regardless of the specific tools used to group alleles, the trial would then test the hypothesis that a statistically significant difference in response to a treatment can be demonstrated between two groups of patients each defined by the presence of zero, one or two alleles (or allele groups) at a gene or genes. Said response may be a desired or an  
10 undesired response. In a preferred embodiment, the treatment protocol involves a comparison of placebo vs. treatment response rates in two or more genotype-defined groups. For example a group with no copies of an allele may be compared to a group with two copies, or a group with no copies may be compared to a group consisting of those with one or two copies. In this manner different genetic models (dominant, co-dominant, recessive) for the transmission of a treatment response trait  
15 can be tested. Alternatively, statistical methods that do not posit a specific genetic model, such as contingency tables, can be used to measure the effects of an allele on treatment response.

In another preferred embodiment, patients in a clinical trial can be grouped  
20 (at the end of the trial) according to treatment response, and statistical methods can be used to compare allele (or genotype or haplotype) frequencies in two groups. For example responders can be compared to nonresponders, or patients suffering adverse events can be compared to those not experiencing such effects. Alternatively response data can be treated as a continuous variable and the ability of genotype to  
25 predict response can be measured. In a preferred embodiments patients who exhibit extreme phenotypes are compared with all other patients or with a group of patients who exhibit a divergent extreme phenotype. For example if there is a continuous or semi-continuous measure of treatment response (for example the Alzheimer's Disease Assessment Scale, the Mini-Mental State Examination or the Hamilton  
30 Depression Rating Scale) then the 10% of patients with the most favorable responses could be compared to the 10% with the least favorable, or the patients one standard deviation above the mean score could be compared to the remainder, or to those one standard deviation below the mean score. One useful way to select the threshold for defining a response is to examine the distribution of responses in a placebo group. If  
35 the upper end of the range of placebo responses is used as a lower threshold for an 'outlier response' then the outlier response group should be almost free of placebo responders. This is a useful threshold because the inclusion of placebo responders in

a 'true' reponse group decreases the ability of statistical methods to detect a genetic difference between responders and nonresponders.  
disease.

In a related aspect, the invention provides a method for developing a disease management protocol that entails diagnosing a patient with a disease or a disease susceptibility, determining the genotype of the patient at a gene or genes correlated with treatment response and then selecting an optimal treatment based on the disease and the genotype (or genotypes or haplotypes). The disease management protocol may be useful in an education program for physicians, other caregivers or pharmacists; may constitute part of a drug label; or may be useful in a marketing campaign.

In a related aspect, the invention provides a method for treating a patient at risk for or diagnosed with drug-induced disease or pathological condition or dysfunction using the methods of the above aspect and conducting a step c) which involves determining the gene allele load status of the patient. This method further involves converting the data obtained in steps b) and c) into a treatment protocol that includes a comparison of the allele status determinations of these steps with the allele frequency of a control population. This affords a statistical calculation of the patient's risk for having drug-induced disease, disorder or dysfunction. In a preferred embodiment, the method is useful for identifying drug-induced disease, disorder or dysfunction. In addition, in related embodiments, the methods provide a treatment protocol that predicts a patient to be at high risk for drug-induced disease, disorder or dysfunction responding by exhibiting signs and symptoms of drug-induced toxicity, disorders, dysfunction if the patient is determined as having a genotype or allelic difference in the identified gene or genes. Such patients are preferably given alternative therapies.

The invention also provides a method for improving the safety of candidate therapies for the identification of a drug-induced disease, disorder, or dysfunction. The method includes the step of comparing the relative safety of the candidate therapeutic intervention in patients having different alleles in one or more than one of the genes listed in Tables 1-6, 12-17, and 18-23. Preferably, administration of the drug is preferentially provided to those patients with an allele type associated with increased efficacy. In a preferred embodiment, the alleles of identified gene or genes used are wild-type and those associated with altered biological activity.

For the aspects above, in connection with any of the listed diseases, disorders, or conditions and treatments thereof, or indeed any disease or disorder, can utilize pharmacogenetic information and determinations of genes and gene pathways involved in the absorption, distribution, metabolism, or excretion of said

treatment. Thus, the presence or the absence of at least variance or haplotype in such a gene or genes can be indicative of the effectiveness of a treatment for a given disease, disorder, or condition, where the gene or gene pathway is involved in the absorption, distribution, metabolism, or excretion of said treatment, e.g., a drug treatment.

As used herein, by “therapy associated with drug-induced disease” is meant any therapy resulting in pathophysiologic dysfunction or signs and symptoms of failure or dysfunction, or those associated with the pathophysiological manifestations of a disorder. A suitable therapy can be a pharmacological agent, drug, or therapy that alters a pathways identified to affect the molecular structure or function of the parent candidate therapeutic intervention thereby affecting drug-induced disease or disorder progression of any of the described organ system dysfunctions.

By “drug-induced disease” or “drug-induced syndrome” is meant any physiologic condition that may be correlated with medical therapy by a drug, agent, or candidate therapeutic intervention.

By “drug-induced dysfunction” is meant a physiologic disorder or syndrome that may be correlated with medical therapy by a drug, agent, or candidate therapeutic intervention in which symptomology is similar to drug-induced disease. Specifically included are: a) hemostasis dysfunction; b) cutaneous disorders; c) cardiovascular dysfunction; d) renal dysfunction; e) pulmonary dysfunction; f) hepatic dysfunction; g) systemic reactions; and h) central nervous system dysfunction.

By “drug associated disorder” is meant a physiologic dysfunction that may be correlated with medical therapy by a drug, agent, or candidate therapeutic intervention. The drug associated disorder may include disease, disorder, or dysfunction.

As used herein, by “therapy associated with inflammatory or immunological disease” is meant any therapy resulting in dysfunction or signs and symptoms of a inflammatory or immunologic condition or dysfunction, or those associated with the pathophysiological manifestations of a clinically diagnosed inflammatory or immunologic disorder or syndrome. A suitable therapy can be a pharmacological agent or drug that may enhance or inhibit metabolic pathways identified to affect the molecular structure or function of the parent candidate therapeutic intervention thereby affecting inflammatory or immunological disease progression of any of these inflammatory or immunological dysfunctions.

By “inflammatory or immunological dysfunction” is meant a disease or syndrome in which symptomology is similar to a inflammatory or immunological

disease. Specifically included are: arthritis, asthma, chronic obstructive pulmonary disease, autoimmune disease, inflammatory bowel disease, immunosuppression related to transplantation, pain associated with inflammation, psoriasis, atherosclerosis, and hepatitis.

5 By "pathway" or "gene pathway" is meant the group of biologically relevant genes involved in a pharmacodynamic or pharmacokinetic mechanism of drug, agent, or candidate therapeutic intervention. These mechanisms may further include any physiologic effect the drug or candidate therapeutic intervention renders.

10 By "disease management protocol" or "treatment protocol" is meant a means for devising a therapeutic plan for a patient using laboratory, clinical and genetic data, including the patient's diagnosis and genotype. The protocol clarifies therapeutic options and provides information about probable prognoses with different treatments. The treatment protocol may the provide an estimate of the likelihood that a patient will respond positively or negatively to a therapeutic  
15 intervention. The treatment protocol may also provide guidance regarding optimal drug dose and administration, and likely timing of recovery or rehabilitation. A "disease management protocol" or "treatment protocol" may also be formulated for asymptomatic and healthy subjects in order to forecast future disease risks based on laboratory, clinical and genetic variables. In this setting the protocol specifies  
20 optimal preventive or prophylactic interventions, including use of compounds, changes in diet or behavior, or other measures. The treatment protocol may include the use of a computer program.

In another aspect, the invention provides a kit containing at least one probe or at least one primer (or other amplification oligonucleotide) or both (e.g., as described  
25 above) corresponding to a gene or genes listed in Tables 1-6, 12-17, and 18-23 or other gene related to a disease or condition listed in Tables 7-11 or described within the invention. The kit is preferably adapted and configured to be suitable for identification of the presence or absence of a particular variance or variances, which can include or consist of a nucleic acid sequence corresponding to a portion of a gene. A plurality of variances  
30 may comprise a haplotype of haplotypes. The kit may also contain a plurality of either or both of such probes and/or primers, e.g., 2, 3, 4, 5, 6, or more of such probes and/or primers. Preferably the plurality of probes and/or primers are adapted to provide detection of a plurality of different sequence variances in a gene or plurality of genes, e.g., in 2, 3, 4, 5, or more genes or to amplify and/or sequence a nucleic acid sequence  
35 including at least one variance site in a gene or genes. Preferably one or more of the variance or variances to be detected are correlated with variability in a treatment response or tolerance, and are preferably indicative of an effective response to a treatment. In preferred embodiments, the kit contains components (e.g., probes and/or primers) adapted

or useful for detection of a plurality of variances (which may be in one or more genes) indicative of the effectiveness of at least one treatment, preferably of a plurality of different treatments for a particular disease or condition. It may also be desirable to provide a kit containing components adapted or useful to allow detection of a plurality of variances indicative of the effectiveness of a treatment or treatment against a plurality of diseases. The kit may also optionally contain other components, preferably other components adapted for identifying the presence of a particular variance or variances. Such additional components can, for example, independently include a buffer or buffers, e.g., amplification buffers and hybridization buffers, which may be in liquid or dry form, a DNA polymerase, e.g., a polymerase suitable for carrying out PCR (e.g., a thermostable DNA polymerase), and deoxy nucleotide triphosphates (dNTPs). Preferably a probe includes a detectable label, e.g., a fluorescent label, enzyme label, light scattering label, or other label. Preferably the kit includes a nucleic acid or polypeptide array on a solid phase substrate. The array may, for example, include a plurality of different antibodies, and/or a plurality of different nucleic acid sequences. Sites in the array can allow capture and/or detection of nucleic acid sequences or gene products corresponding to different variances in one or more different genes. Preferably the array is arranged to provide variance detection for a plurality of variances in one or more genes which correlate with the effectiveness of one or more treatments of one or more diseases, which is preferably a variance as described herein.

The kit may also optionally contain instructions for use, which can include a listing of the variances correlating with a particular treatment or treatments for a disease or diseases and/or a statement or listing of the diseases for which a particular variance or variances correlates with a treatment efficacy and/or safety.

Preferably the kit components are selected to allow detection of a variance described herein, and/or detection of a variance indicative of a treatment, e.g., administration of a drug, pointed out herein.

Additional configurations for kits of this invention will be apparent to those skilled in the art.

The invention also includes the use of such a kit to determine the genotype(s) of one or more individuals with respect to one or more variance sites in one or more genes identified herein. Such use can include providing a result or report indicating the presence and/or absence of one or more variant forms or a gene or genes which are indicative of the effectiveness of a treatment or treatments.



In another aspect, the invention provides a method for determining whether there is a genetic component to intersubject variation in a surrogate treatment response. The method involves administering the treatment to a group of related (preferably normal) subjects and a group of unrelated (preferably normal) subjects, measuring a surrogate pharmacodynamic or pharmacokinetic drug response variable in the subjects, performing a statistical test measuring the variation in response in the group of related subjects and, separately in the group of unrelated subjects, comparing the magnitude or pattern of variation in response or both between the groups to determine if the responses of the groups are different, using a predetermined statistical measure of difference. A difference in response between the groups is indicative that there is a genetic component to intersubject variation in the surrogate treatment response.

In preferred embodiments, the size of the related and unrelated groups is set in order to achieve a predetermined degree of statistical power.

In another aspect, the invention provides a method for evaluating the combined contribution of two or more variances to a surrogate drug response phenotype in subjects (preferably normal subjects) by a. genotyping a set of unrelated subjects participating in a Phase I trial of a compound. The genotyping is for two or more variances (which can be a haplotype), thereby identifying subjects with specific genotypes, where the two or more specific genotypes define two or more genotype-defined groups. A drug is administered to subjects with two or more of the specific genotypes, and a surrogate pharmacodynamic or pharmacokinetic drug response variable is measured in the subjects. A statistical test or tests is performed to measure response in the groups separately, where the statistical tests provide a measurement of variation in response with each group. The magnitude or pattern of variation in response or both is compared between the groups to determine if the groups are different using a predetermined statistical measure of difference.

In preferred embodiments, the specific genotypes are homozygous genotypes for two variances. In preferred embodiments, the comparison is between groups of subjects differing in three or more variances, e.g., 3, 4, 5, 6, or even more variances.

In another aspect, the invention provides a method for providing contract research services to clients (preferably in the pharmaceutical and biotechnology industries), by enrolling subjects (e.g., normal and/or patient subjects) in a clinical

drug trial or study unit (preferably a Phase I drug trial or study unit) for the purpose of genotyping the subjects in order to assess the contribution of genetic variation to variation in drug response, genotyping the subjects to determine the status of one or more variances in the subjects, administering a compound to the subjects and  
5 measuring a surrogate drug response variable, comparing responses between two or more genotype-defined groups of subjects to determine whether there is a genetic component to the interperson variability in response to said compound; and reporting the results of the Phase I drug trial to a contracting entity. Clearly, intermediate results, e.g., response data and/or statistical analysis of response or  
10 variation in response.

In preferred embodiments, at least some of the subjects have disclosed that they are related to each other and the genetic analysis includes comparison of groups of related individuals. To encourage participation of sufficient numbers of related individuals, it can be advantageous to offer or provide compensation to one or more  
15 of the related individuals based on the number of subjects related to them who participate in the clinical trial, or on whether at least a minimum number of related subjects participate, e.g., at least 3, 5, 10, 20, or more.

In a related aspect, the invention provides a method for recruiting a clinical trial population for studies of the influence of genetic variation on drug response, by  
20 soliciting subjects to participate in the clinical trial, obtaining consent of each of a set of subjects for participation in the clinical trial, obtaining additional related subjects for participation in the clinical trial by compensating one or more of the related subjects for participation of their related subjects at a level based on the number of related subjects participating or based on participation of at least a  
25 minimum specified number of related subjects, e.g., at minimum levels as specified in the preceding aspect.

In all of the aspects herein, the gene (or genes) can be a gene as identified herein (e.g., in the Detailed Description, including examples, or Tables 1-6, 12-17, or 18-23, or is in a pathway as identified herein, e.g., in a Table.

30 By "pathway" or "gene pathway" is meant the group of biologically relevant genes involved in a pharmacodynamic or pharmacokinetic mechanism of drug, agent, or candidate therapeutic intervention. These mechanisms may further include any physiologic effect the drug or candidate therapeutic intervention renders.

Included in this are "biochemical pathways" which is used in its usual sense to refer to a series of related biochemical processes (and the corresponding genes and gene products) involved in carrying out a reaction or series of reactions. Generally in a cell, a pathway performs a significant process in the cell.

5 By "pharmacological activity" used herein is meant a biochemical or physiological effect of drugs, compounds, agents, or candidate therapeutic interventions upon administration and the mechanism of action of that effect.

The pharmacological activity is then determined by interactions of drugs, compounds, agents, or candidate therapeutic interventions, or their mechanism of action, on their target proteins or macromolecular components. By "agonist" or "mimetic" or "activators" is meant a drug, agent, or compound that activate physiologic components and mimic the effects of endogenous regulatory compounds. By "antagonists", "blockers" or "inhibitors" is meant drugs, agents, or compounds that bind to physiologic components and do not mimic endogenous regulatory compounds, or interfere with the action of endogenous regulatory compounds at physiologic components. These inhibitory compounds do not have intrinsic regulatory activity, but prevent the action of agonists. By "partial agonist" or "partial antagonist" is meant an agonist or antagonist, respectively, with limited or partial activity. By "negative agonist" or "inverse antagonists" is meant that a drug, compound, or agent that can interact with a physiologic target protein or macromolecular component and stabilizes the protein or component such that agonist-dependent conformational changes of the component do not occur and agonist mediated mechanism of physiological action is prevented. By "modulators" or "factors" is meant a drug, agent, or compound that interacts with a target protein or macromolecular component and modifies the physiological effect of an agonist.

As used herein the term "chemical class" refers to a group of compounds that share a common chemical scaffold but which differ in respect to the substituent groups linked to the scaffold. Examples of chemical classes of drugs include, for example, phenothiazines, piperidines, benzodiazepines and aminoglycosides.

30 Members of the phenothiazine class include, for example, compounds such as chlorpromazine hydrochloride, mesoridazine besylate, thioridazine hydrochloride, acetophenazine maleate trifluoperazine hydrochloride and others, all of which share a phenothiazine backbone. Members of the piperidine class include, for example,

compounds such as meperidine, diphenoxylate and loperamide, as well as phenylpiperidines such as fentanyl, sufentanil and alfentanil, all of which share the piperidine backbone. Chemical classes and their members are recognized by those skilled in the art of medicinal chemistry.

5 As used herein the term "surrogate marker" refers to a biological or clinical parameter that is measured in place of the biologically definitive or clinically most meaningful parameter. In comparison to definitive markers, surrogate markers are generally either more convenient, less expensive, provide earlier information or provide pharmacological or physiological information not directly obtainable with  
10 definitive markers. Examples of surrogate biological parameters: (i) testing erythrocyte membrane acetylcholinesterase levels in subjects treated with an acetylcholinesterase inhibitor intended for use in Alzheimer's disease patients (where inhibition of brain acetylcholinesterase would be the definitive biological parameter); (ii) measuring levels of CD4 positive lymphocytes as a surrogate marker  
15 for response to a treatment for acquired immune deficiency syndrome (AIDS). Examples of surrogate clinical parameters: (i) performing a psychometric test on normal subjects treated for a short period of time with a candidate Alzheimer's compound in order to determine if there is a measurable effect on cognitive function. The definitive clinical test would entail measuring cognitive function in a clinical  
20 trial in Alzheimer's disease patients. (ii) Measuring blood pressure as a surrogate marker for myocardial infarction. The measurement of a surrogate marker or parameter may be an endpoint in a clinical study or clinical trial, hence "surrogate endpoint".

As used herein the term "related" when used with respect to human subjects  
25 indicates that the subjects are known to share a common line of descent; that is, the subjects have a known ancestor in common. Examples of preferred related subjects include sibs (brothers and sisters), parents, grandparents, children, grandchildren, aunts, uncles, cousins, second cousins and third cousins. Subjects less closely related than third cousins are not sufficiently related to be useful as "related"  
30 subjects for the methods of this invention, even if they share a known ancestor, unless some related individuals that lie between the distantly related subjects are also included. Thus, for a group of related individuals, each subject shares a known ancestor within three generations or less with at least one other subject in the group,

and preferably with all other subjects in the group or has at least that degree of consanguinity due to multiple known common ancestors. More preferably, subjects share a common ancestor within two generations or less, or otherwise have equivalent level of consanguinity. Conversely, as used herein the term “unrelated”,  
5 when used in respect to human subjects, refers to subjects who do not share a known ancestor within 3 generations or less, or otherwise have known relatedness at that degree.

As used herein the term “pedigree” refers to a group of related individuals, usually comprising at least two generations, such as parents and their children, but  
10 often comprising three generations (that is, including grandparents or grandchildren as well). The relation between all the subjects in the pedigree is known and can be represented in a genealogical chart.

As used herein the term “hybridization”, when used with respect to DNA fragments or polynucleotides encompasses methods including both natural  
15 polynucleotides, non-natural polynucleotides or a combination of both. Natural polynucleotides are those that are polymers of the four natural deoxynucleotides (deoxyadenosine triphosphate [dA], deoxycytosine triphosphate [dC], deoxyguanine triphosphate [dG] or deoxythymidine triphosphate [dT], usually designated simply thymidine triphosphate [T]) or polymers of the four natural ribonucleotides  
20 (adenosine triphosphate [A], cytosine triphosphate [C], guanine triphosphate [G] or uridine triphosphate [U]). Non-natural polynucleotides are made up in part or entirely of nucleotides that are not natural nucleotides; that is, they have one or more modifications. Also included among non-natural polynucleotides are molecules related to nucleic acids, such as peptide nucleic acid [PNA]). Non-natural  
25 polynucleotides may be polymers of non-natural nucleotides, polymers of natural and non-natural nucleotides (in which there is at least one non-natural nucleotide), or otherwise modified polynucleotides. Non-natural polynucleotides may be useful because their hybridization properties differ from those of natural polynucleotides. As used herein the term “complementary”, when used in respect to DNA fragments,  
30 refers to the base pairing rules established by Watson and Crick: A pairs with T or U; G pairs with C. Complementary DNA fragments have sequences that, when aligned in antiparallel orientation, conform to the Watson-Crick base pairing rules at all positions or at all positions except one. As used herein, complementary DNA

fragments may be natural polynucleotides, non-natural polynucleotides, or a mixture of natural and non-natural polynucleotides.

As used herein "amplify" when used with respect to DNA refers to a family of methods for increasing the number of copies of a starting DNA fragment.

5 Amplification of DNA is often performed to simplify subsequent determination of DNA sequence, including genotyping or haplotyping. Amplification methods include the polymerase chain reaction (PCR), the ligase chain reaction (LCR) and methods using Q beta replicase, as well as transcription-based amplification systems such as the isothermal amplification procedure known as self-sustained sequence  
10 replication (3SR, developed by T.R. Gingeras and colleagues), strand displacement amplification (SDA, developed by G.T. Walker and colleagues) and the rolling circle amplification method (developed by P. Lizardi and D. Ward).

As used herein "contract research services for a client" refers to a business arrangement wherein a client entity pays for services consisting in part or in whole  
15 of work performed using the methods described herein. The client entity may include a commercial or non-profit organization whose primary business is in the pharmaceutical, biotechnology, diagnostics, medical device or contract research organization (CRO) sector, or any combination of those sectors. Services provided to such a client may include any of the methods described herein, particularly  
20 including clinical trial services, and especially the services described in the Detailed Description relating to a Pharmacogenetic Phase I Unit. Such services are intended to allow the earliest possible assessment of the contribution of a variance or variances or haplotypes, from one or more genes, to variation in a surrogate marker in humans. The surrogate marker is generally selected to provide information on a  
25 biological or clinical response, as defined above.

As used herein, "comparing the magnitude or pattern of variation in response" between two or more groups refers to the use of a statistical procedure or procedures to measure the difference between two different distributions. For example, consider two genotype-defined groups, AA and aa, each homozygous for a  
30 different variance or haplotype in a gene believed likely to affect response to a drug. The subjects in each group are subjected to treatment with the drug and a treatment response is measured in each subject (for example a surrogate treatment response). One can then construct two distributions: the distribution of responses in the AA

group and the distribution of responses in the aa group. These distributions may be compared in many ways, and the significance of any difference qualified as to its significance (often expressed as a p value), using methods known to those skilled in the art. For example, one can compare the means, medians or modes of the two distributions, or one can compare the variance or standard deviations of the two distributions. Or, if the form of the distributions is not known, one can use nonparametric statistical tests to test whether the distributions are different, and whether the difference is significant at a specified level (for example, the  $p < 0.05$  level, meaning that, by chance, the distributions would differ to the degree measured less than one in 20 similar experiments). The types of comparisons described are similar to the analysis of heritability in quantitative genetics, and would draw on standard methods from quantitative genetics to measure heritability by comparing data from related subjects.

Another type of comparison that can be usefully made is between related and unrelated groups of subjects. That is, the comparison of two or more distributions is of particular interest when one distribution is drawn from a population of related subjects and the other distribution is drawn from a group of unrelated subjects, both subjected to the same treatment. (The related subjects may consist of small groups of related subjects, each compared only to their relatives.) A comparison of the distribution of a drug response variable (e.g. a surrogate marker) between two such groups may provide information on whether the drug response variable is under genetic control. For example, a narrow distribution in the group(s) of related subjects (compared to the unrelated subjects) would tend to indicate that the measured variable is under genetic control (i.e. the related subjects, on account of their genetic homogeneity, are more similar than the unrelated individuals). The degree to which the distribution was narrower in the related individuals (compared to the unrelated individuals) would be proportionate to the degree of genetic control. The narrowness of the distribution could be quantified by, for example, computing variance or standard deviation. In other cases the shape of the distribution may not be known and nonparametric tests may be preferable. Nonparametric tests include methods for comparing medians such as the sign test, the slippage test, or the rank correlation coefficient (the nonparametric equivalent of the ordinary correlation

coefficient). Pearson's Chi square test for comparing an observed set of frequencies with an expected set of frequencies can also be useful.

In addition to and in connection with the determination and utilization of pharmacogenetic information for treatment of proliferative disorders such as cancer, information provided by and genes identified in the following patents and applications are useful: Housman, INHIBITORS OF ALTERNATIVE ALLELES OF GENES ENCODING PROTEINS VITAL FOR CELL VIABILITY OR CELL GROWTH AS A BASIS FOR CANCER THERAPEUTIC AGENTS, U.S. Patent 5,702,890, issued December 30, 1997, and Housman et al., PCT/US98/05419, entitled TARGET GENES FOR ALLELE-SPECIFIC DRUGS. Essential and conditionally essential genes identified therein can be utilized as targets for the methods and compositions described in those documents. As an example of the use of the information provided by the listed references, LOH affecting a particular target gene provides information on the effect of a particular variance or variances in that target gene. This can be extended to evaluation of the effects of combinations of variations one or more genes subject to LOH. The utilization of conditionally essential genes is described further herein. For complete description, see the respective patent and application.

The inventors have also determined that the loss of chromosomes or chromosome segments that is characteristic of cancer cells (often termed loss of heterozygosity, or LOH) has an important interaction with gene sequence variances, in determining the effect of a treatment on a patient's cancer cells. Cancer cells with LOH may have only one copy of a gene that is present in two copies in normal cells. If the two normal copies (one inherited from each parent) differ in activity in a given patient, then the cancer cells will be functionally different from the normal cells on account of having only one of the two copies. For example, consider a patient heterozygous for high and low activity forms of a gene that metabolizes a cancer drug. If LOH involving the chromosome containing the gene has left cancer cells with only one copy of the gene then the metabolism of the drug will be different in cancer cells compared to normal cells. If the gene copy that is lost by LOH is the high activity version then cancer cells may experience higher levels of drug (due to slower metabolism) than normal cells. Provided in this invention are specific chromosomal sites characterized by LOH, and the frequency of LOH in different types of neoplasia at said sites. These LOH sites, in conjunction with the variances described above, may prove more useful in predicting response to treatment than variances alone. Methods for determining the combined impact of LOH and variances are described herein.



It was recognized that environmental factors can cause certain genes to be essential that are not essential under other conditions (including usual *in vivo* and culture conditions). For example, certain genes involved in intermediary metabolism are not essential if the cell or organism is supplemented with high concentrations of a particular nutrient or chemical entity, but if that nutrient or chemical entity is absent or present at low levels, the gene product is essential. In another example, the administration of a drug that inhibits one or more functions within the cell can cause other functions to be essential that are not essential in the absence of the drug. In another example, subjecting a cell to harsh physical agents, such as radiation, can cause certain genes to be essential that are not essential under normal conditions. Such genes are essential under certain conditions associated with the therapy of cancer. The demonstration that such genes are present in the population in more than one allelic form and are subjected to loss of heterozygosity in cancer or noncancer proliferative disorders makes such genes targets for allele specific drugs for the treatment of such disorders.

It was found that such genes, similar to generally essential genes, are frequently deleted due to LOH in cells of proliferative disorders such as cancers. Treatment methods involving such genes can provide enhanced sensitivity of cancer cells to a variety of different anti-proliferative treatments, including radiation and administration of various compounds. Unless otherwise indicated, the term "essential" includes both strictly essential and beneficial to cell growth or survival.

A gene is said to be "conditionally essential" if it is essential for cell survival or proliferation in a specific environmental condition differing from usual *in vivo* conditions or usual culture conditions for the type of cell, where the specific environmental condition is caused by the presence or absence of specific environmental constituents, pharmaceutical agents, including small molecules or biologicals, or physical factors such as radiation, or if the gene enhances the growth or survival of the cell under such conditions by at least 2-fold, preferably by at least 4-fold, and more preferably by at least 6-fold, 10-fold or even more.

Cancer cells, as well as cells from a number of different non-malignant proliferative disorders, from an individual almost invariably undergo a loss of genetic material (DNA) when compared to normal cells. Frequently, this deletion of genetic material includes the loss of one of the two alleles of genes for which the normal somatic cells of the same individual are heterozygous, meaning that there are differences in the sequence of the gene on each of the parental chromosomes. The loss of one allele in the cancer cells is referred to as "loss of heterozygosity" (LOH). Recognizing that almost all, if not all, varieties of cancer undergo LOH, and that regions of DNA loss are often quite extensive, the genetic content of deleted regions

in cancer cells was evaluated and it was found that a variety of different conditionally essential genes are frequently deleted, reducing the cancer cell to only one copy. In this context, the term "deleted" refers to the loss of one of two copies of a chromosome or sub-chromosomal segment. Further investigation demonstrated that the loss of genetic material from cancer cells sometimes results in the selective loss of one of two alleles of a particular gene at a particular locus or loci on a particular chromosome.

The term "proliferative disorder" refers to various cancers and disorders characterized by abnormal growth of somatic cells leading to an abnormal mass of tissue which exhibits abnormal proliferation, and consequently, the growth of which exceeds and is uncoordinated with that of the normal tissues. The abnormal mass of cells is referred to as a "tumor", where the term tumor can include both localized cell masses and dispersed cells. The term "cancer" refers to a neoplastic growth and is synonymous with the terms "malignancy", or "malignant tumor". The treatment of cancers and the identification of anticancer agents is the concern of particularly preferred embodiments of the aspects of the present invention. Other abnormal proliferative diseases include "nonmalignant tumors", and "dysplastic" conditions including, but not limited to, leiomyomas, endometriosis, benign prostate hypertrophy, atherosclerotic plaques, and dysplastic epithelium of lung, breast, cervix, or other tissues. Drugs used in treating cancer and other non-cancer proliferative disorders commonly aim to inhibit the proliferation of cells and are commonly referred to as antiproliferative agents.

"Loss of heterozygosity", "LOH", or "allele loss" refers to the loss of one of the alleles of a gene from a cell or cell lineage previously having two alleles of that gene. Normal cells contain two copies of each gene, one inherited from each parent. When these two genes differ in their gene sequence, the cell is said to be "heterozygous". The term heterozygous indicates that a cell contains two different allelic forms of a particular gene and thus indicates that the allelic forms differ at at least one sequence variance site. When one allele is lost in a cell, that cell and its progeny cells, comprising its cell lineage, become "hemizygous" for that gene or "partially hemizygous" for a set of genes, and heterozygosity is lost. LOH occurs in all cancers and is a common characteristic of non-malignant, proliferative disorders. In general, many different genes will be affected by loss of heterozygosity in a cell which undergoes loss of heterozygosity. In many cancers 10-40% of all of the genes in the human genome (there are estimated to be 60,000-100,000 different genes in the genome) will exhibit LOH. In the context of this invention, these terms refer preferably to loss of heterozygosity of a gene that has a particular sequence variance in normal somatic cells of an individual such that there is loss of heterozygosity with

respect to that particular sequence variance. Also preferably, these terms refer to loss of heterozygosity of a particular sequence variance that is recognized by an inhibitor that will inhibit one allele of the gene present in normal cells of the individual, but not an alternative allele.

5 The present invention provides a number of advantages. For example, the methods described herein allow for use of a determination of a patient's genotype for the timely administration of the most suitable therapy for that particular patient. The methods of this invention provide a basis for successfully developing and  
10 obtaining regulatory approval for a compound even though efficacy or safety of the compound in an unstratified population is not adequate to justify approval. From the point of view of a pharmaceutical or biotechnology company, the information obtained in pharmacogenetic studies of the type described herein could be the basis of a marketing campaign for a drug. For example, a marketing campaign that  
15 emphasized the superior efficacy or safety of a compound in a genotype or haplotype restricted patient population, compared to a similar or competing compound used in an undifferentiated population of all patients with the disease. In this respect a marketing campaign could promote the use of a compound in a genetically defined subpopulation, even though the compound was not intrinsically  
20 superior to competing compounds when used in the undifferentiated population with the target disease. In fact even a compound with an inferior profile of action in the undifferentiated disease population could become superior when coupled with the appropriate pharmacogenetic test.

By "comprising" is meant including, but not limited to, whatever follows the  
25 word "comprising". Thus, use of the term "comprising" indicates that the listed elements are required or mandatory, but that other elements are optional and may or may not be present. By "consisting of" is meant including, and limited to, whatever follows the phrase "consisting of". Thus, the phrase "consisting of" indicates that the listed elements are required or mandatory, and that no other elements may be  
30 present. By "consisting essentially of" is meant including any elements listed after the phrase, and limited to other elements that do not interfere with or contribute to the activity or action specified in the disclosure for the listed elements. Thus, the phrase "consisting essentially of" indicates that the listed elements are required or mandatory, but that other elements are optional and may or may not be present  
35 depending upon whether or not they affect the activity or action of the listed elements.

Other features and advantages of the invention will be apparent from the following description of the preferred embodiments thereof, and from the claims.

## DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

First a brief description of the Tables is provided.

**Tables 1-6.** Gene Tables, lists genes that may be involved in  
5 pharmacological response to cancer or other neoplastic disorders, neurological and  
psychiatric, adsorption, distribution, metabolism, or excretion of, inflammation and  
immune, endocrine and metabolism, and cardiovascular and renal therapeutics,  
respectively, or that may define disease subsets with different prognosis and  
consequent implications for treatment. These tables have seven columns. Column  
10 1, headed "Class" provides broad groupings of genes relevant to the pharmacology  
of indication-specific drugs. Column 2, headed "Pathway", provides a more detailed  
categorization of the different classes of genes by indicating the overall purpose of  
large groups of genes. These pathways contain genes implicated in the etiology or  
treatment response of the various diseases detailed in Tables 7-11. Column 3,  
15 headed "Function", further categorizes the pathways listed in column 2. Some  
categories in column 2 (e.g. "Clotting") are not further categorized in column 3.

In column 4, headed "Name", lists the genes belonging to the class, pathway  
and function shown to the left (in columns 1 – 3). The gene names given are  
generally those used in the OMIM database or in GenBank, however one skilled in  
20 the art will recognize that many genes have more than one name, and that it is a  
straightforward task to identify synonymous names. For example, many alternate  
gene names are provided in the OMIM record for a gene.

In column 5, headed "OMIM", the Online Mendelian Inheritance in Man  
(OMIM) record number is listed for each gene in column 4. This record number  
25 can be entered next to the words: "Enter one or more search keywords:" at the  
OMIM world wide web site. The url is:  
<http://www3.ncbi.nlm.nih.gov/Omim/searchomim.html>. An OMIM record exists for  
most characterized human genes. The record often has useful information on the  
chromosome location, function, alleles, and human diseases or disorders associated  
30 with each gene.

In column 6, headed "GID", provides the GenBank identification number  
(hence GID) of a genomic, cDNA, or partial sequence of the gene named in column  
4. Usually the GID provides the record of a cDNA sequence. Many genes have  
multiple Genbank accession numbers, representing different versions of a sequence  
35 obtained by different research groups, or corrected or updated versions of a  
sequence. As with the gene name, one skilled in the art will recognize that  
alternative GenBank records related to the named record can be obtained easily. All  
other GenBank records listing sequences that are alternate versions of the sequences

named in the table are equally suitable for the inventions described in this application. (One straightforward way to obtain additional GenBank records for a gene is on the internet. General instructions can be found at the NCBI web site at: <http://www3.ncbi.nlm.nih.gov>. More specifically, the GenBank record number in column 6 can be entered at the url:

<http://www3.ncbi.nlm.nih.gov/Entrez/nucleotide.html>. Once the GenBank record has been retrieved one can click on the “nucleotide neighbors” link and additional GenBank records from the same gene will be listed.action,

Column 7, headed “locus”, provides the chromosome location of the gene listed on the same row. The chromosome location helps confirm the identity of the named gene if there is any ambiguity.

**Tables 7-11** are matrix tables showing the intersection of genes and therapeutic indications – that is, which categories of genes are most likely to account for interpatient variation in response to treatments for which diseases. The first two columns provide a framework for organizing the genes listed in Tables 1-6. Column 1 is similar to the ‘Class’ column in Tables 1-6, while column 2 is a combination of the ‘Pathway’ and ‘Function’ columns in Tables 1-6. It is intended that the summary terms listed in columns 1 and 2 be read as referring to all the genes in the corresponding sections of Tables 1-6. The remaining columns in Tables 7-11 list the specific indications for a given disease category, for example in Table 7 there are thirteen neurological and psychiatric indications. The information in the Tables lies in the shaded boxes at the intersection of various ‘Pathways’ (the rows) and treatment indications. An intersection box is shaded when a row corresponding to a particular pathway (and by extension all the genes listed in that pathway in Tables 1-6) intersects a column for a specific neurological or psychiatric disease such that the pathway and genes are of possible use in explaining interpatient differences in response to treatments for the neurological or psychiatric indication.. Thus, the Tables enables one skilled in the art to identify therapeutically relevant genes in patients with one of the listed indications for the purposes of stratification of these patients based upon genotype and subsequent correlation of genotype with drug response. The shaded intersections indicate preferred sets of genes for understanding the basis of interpatient variation in response to therapy of the indicated disease indication, and in that respect are exemplary. Any of the genes in the tables may account for interpatient variation in response to treatments for any of the diseases listed. Thus, the shaded boxes indicate the gene pathways that one skilled in the art would first investigate in trying to understand interpatient variation in response to therapy for the listed neurological indications.

**Tables 12-17** lists the exemplary DNA sequence variances in genes for therelevant to the methods described in the present invention. These variances were discovered by the inventors in studies of selected genes listed in Tables 1-6, and are provided here as useful for the methods of the present invention. The variances in  
5 Tables 12-17 were discovered by one or more of the methods described below in the Detailed Description or Examples. The tables have eight columns. The column headings are spread over two rows, with five headings in the first row and three in the second row. The gene sequence variance listings in the tables have a similar organization to the column headings, with a set of nomenclature data in the first row  
10 for each gene entry, and variance data in the second and additional following rows for however many sequence variances are available for a specific gene. Column 1, the "Name" column, contains the Human Genome Organization (HUGO) identifier for the gene. Column 2, the "GID" column provides the GenBank accession number of a genomic, cDNA, or partial sequence of a particular gene. Column 3, the  
15 "OMIM\_ID" column contains the record number corresponding to the Online Mendelian Inheritance in Man database for the gene provided in columns 1 and 2. This record number can be entered at the world wide web site <http://www3.ncbi.nlm.nih.gov/Omim/searchomim.html> to search the OMIM record on the gene. Column 4, the VGX\_Symbol column, provides an internal identifier  
20 for the gene. Column 5, the "Description" column provides a descriptive name for the gene, when available. Columns 6, 7 and 8 are on the second row of columns. Column 6, the "Variance\_Start" column provides the nucleotide location of a variance with respect to the first listed nucleotide in the GenBank accession number provided in column 2. That is, the first nucleotide of the GenBank accession is  
25 counted as nucleotide 1 and the variant nucleotide is numbered accordingly. Column 7, the "variance" column provides the nucleotide location of a variance with respect to an ATG codon believed to be the authentic ATG start codon of the gene, where the A of ATG is numbered as one (1) and the immediately preceding nucleotide is numbered as minus one (-1). This reading frame is important because  
30 it allows the potential consequence of the variant nucleotide to be interpreted in the context of the gene anatomy (5' untranslated region, protein coding sequence, 3' untranslated region). Column 7 also provides the identity of the two variant nucleotides at the indicated position. Column 8, the "CDS\_Context" column indicates whether the variance is in a coding region but silent (S); in a coding region and results in an amino acid change (e.g., R347C, where the letters are one letter  
35 amino acid abbreviations and the number is the amino acid residue in the encoded amino acid sequence which is changed); in a sequence 5' to the coding region (5); or in a sequence 3' to the coding region (3). As indicated above, interpreting the

location of the variance in the gene is contingent on the correct assignment of the initial ATG of the encoded protein (the translation start site). It should be recognized that assignment of the correct ATG may occasionally be incorrect in GenBank, but that one skilled in the art will know how to carry out experiments to definitively identify the correct translation initiation codon (which is not always an ATG). In the event of any potential question concerning the proper identification of a gene or part of a gene, due for example, to an error in recording an identifier or the absence of one or more of the identifiers, the priority for use to resolve the ambiguity is GenBank accession number, OMIM identification number, HUGO identifier, common name identifier.

**Tables 18-23** lists additional DNA sequence variances (in addition to those in Tables 12-17) in genes relevant to the methods of the present invention (i.e. selected genes from Tables 1-6). These variances were identified by various research groups and published in the scientific literature. The inventors realized that these variances may be useful for understanding interpatient variation in response to treatment of the diseases listed in Tables 7-11, and more generally useful for the methods of the present invention. The layout of Tables 18-23 is identical to that of Tables 12-17, and therefore the descriptions of the rows and columns in Tables 12-17 (above) pertain to Tables 18-23, as do the caveats and other remarks.

**Tables 24-68** provide lists of exemplary compounds in clinical development for the various disease indications listed in Tables 7-11. The compounds listed in the tables are exemplary; that is, the methods of the invention will apply to other compounds as well. Each table has four columns. The first column is titled "Product Name", the second column is titled "Chemical Name", the third "Action" and the fourth "Indication". Under these headings are listed rows of compounds. For each compound there is a brief summary of information about the product name, its pharmacological action and potential clinical uses. The first column, "Product Name", provides the generic name and/or alphanumeric designation of the compound, as well as its trade name in some cases (in capital letters). The second column, "Chemical Name" provides the full chemical name of the compound. The listed compounds, or compounds chemically related to those listed (e.g. by modification of one or more chemical moieties of the listed compounds), are suitable for the methods of this invention. The third column, "Action", summarizes in a word or phrase an important pharmacological action of the compound, or what is currently believed to be an important pharmacological action – in most cases additional pharmacological actions are known but not listed to conserve space; alternatively, subsequent studies may reveal additional or alternative

pharmacological actions. (Sources listed in the detailed description will help clarify whether additional pharmacological actions have been discovered.) The fourth column, "Indication", provides an exemplary disease or condition for which the compound is currently being, or has already been, developed. In many cases the compound is being, has already been, or will likely be developed for other indications. Again, one skilled in the art will know how to identify additional drug development programs for these compounds. For example, a compound in development for one neurodegenerative disease is likely to be evaluated in the treatment of other neurodegenerative diseases.



## Detailed Description

### Preferred Embodiments

#### I. Disease Indications

##### A. Neurological and Psychiatric Diseases

5           The treatment of neurological and psychiatric diseases presents a challenge to physicians and other medical practitioners because the available therapeutics are only partially effective in only a fraction of patients. Further, many currently used medicines produce serious adverse effects. Therapeutic benefits and toxic side effects have to be balanced in each patient. This requires much attention to drug  
10       selection, dosage adjustment and monitoring for potential adverse events on the part of care givers – effectively a new pharmacokinetic and pharmacodynamic study must be performed for each patient. These limitations of therapy are especially true of the most debilitating neurological and psychiatric diseases such as psychosis, depression, epilepticepilepsy, the neurodegenerative diseases including Alzheimer's  
15       disease and Parkinson's disease, migraine and cerebrovascular disease. Although these diseases have distinct clinical presentations, havethere is extensive overlap in pathogenetic mechanisms and symptoms.

          Difficulties in treating neurological and psychiatric diseases are attributable to factors such as limited understanding of disease condition pathophysiology, lack  
20       of specificity of pathophysiologic changes (i.e. variation in pathophysiologic machanisms in patients with similar clinical presentation) and lack of specificity of therapeutic compounds. Further, most medical therapy is directed to the amelioration of symptoms, not the arrest or reversal of underlying pathophysiologic processes. One good example of the difficulty of developing and marketing  
25       effective treatments is the history of therapeutic candidates for Alzheimer's disease. Out of dozens of candidate treatments tested in clinical trials only two products have been approved for use in the United Statese, and one of them (tacrine; Cognex) has been withdrawn from marketing due to safety problems. Further, the one marketed product (donezepil; Aricept) is only used by a small fraction of eligible patients  
30       because it has a reputation among caregivers and Alzheimer's disease advocacy groups as being ineffective in most patients. Thus a drug that enjoys a monopoly position in a major disease is not a great commercial success because its shortcomings are widely realized.

          In summary, medical management of neurological and psychiatric diseases is  
35       empirical in nature, is only partially effective, and is associated with multiple undesirable side effects. In view of these clinical realities, the use of genetic tests to identify treatment responders, nonresponders, and/or those likely to develop undesirable side effects will have a major impact on use of existing classes of CNS

drugs, as well as on the development and use of new drugs to treat diseases of the central nervous system.

## **B. Pharmacokinetic Parameters and Effects on Efficacy**

The pharmacokinetic parameters with potential effects on efficacy are absorption, distribution, metabolism, and excretion. These parameters affect efficacy broadly by modulating the availability of a compound at the site(s) of action. Interpatient variation in the availability of a compound drug, agent, or candidate therapeutic intervention can result in a reduction of the available compound or more compound at the site of action with a corresponding altered clinical effect. Differences in these parameters, therefore, can be a potential foundation of interpatient variability to drug response.

### **1. Pharmacokinetic Parameters that Result in a Reduction of Available Drug**

- a. Absorption- Depending on the solubility of the drug, and its ability to passively cross membranes is fundamental to the ability of the drug, agent, or candidate therapeutic intervention to effectively enter the circulation and gain access to the principle site of action. For enteral delivery or administration, absorption is a critical first step in the pharmacologic process. Within the gastrointestinal tract, absorption of a drug, agent, or candidate therapeutic intervention can be affected by the pH of the contents, speed of gastric emptying, and presence of chelating or binding molecules to the drug, agent or candidate therapeutic intervention. Each of these parameters can effectively reduce the rate of passive absorption of the drug across the gastrointestinal mucosal membrane.
- b. Distribution- Once absorbed, the drug, agent or candidate therapeutic intervention must be delivered or distributed to the primary site of pharmacologic action. Although distribution is dependent on regional blood flow and cardiac output; distribution may be further affected by the rate and extent of sequestration of the drug into biological spaces that render the product unavailable to the principle or primary site of pharmacologic site of action. For example, many drugs are actively transported into biological compartments. These processes, if over- or under active may affect the availability and hence reduce the efficacy of the product. Further, only unbound drug may be effective to a cell, tissue, or physiological process, and bound product may be transported to a space that is physiologically unrelated to the pharmacologic mechanism of action or may be of deleterious adverse or toxic consequence.

- c. Metabolism- Induction of metabolic enzymes to covalently modify the parent drug, agent or candidate therapeutic intervention may reduce the ability of the parent drug to elicit a pharmacologic action. Metabolism may affect the target active site binding, rate and extent of distribution and excretion, and overall availability of the active molecule.
- d. Excretion- If the excretion of the drug or drug metabolite is rapid, less drug is available to elicit a pharmacologic effect.

## 2. Pharmacokinetic Parameters that Result in More Available Drug.

- a. Absorption- Enhanced absorption of drugs, agents or candidate therapeutic interventions may result in increased drug availability. For example, in some cases of decreased gastric emptying, there is an enhanced degree of absorption by prolonging contact with gastrointestinal mucosal membranes. In others, a change in the solubility of the drug may enhance the passive transport across the gastrointestinal mucosal membrane.
- b. Distribution- Since free drug is the form that renders pharmacologic action and is metabolised and excreted, drug binding may serve to protect the drug from mechanisms of inactivation. The rate and extent of drug binding affects the free drug concentration relative to the total concentration.
- c. Metabolism- If drug metabolism induction is occurring and the inducer is rapidly removed without adjustment in the dose of the drug, drug metabolism may be decreased and adverse effects or toxicities may occur.
- d. Excretion- If inhibition of active transport of the parent drug or metabolite across the bile cannicula or the renal tubule, there is a net result of enhanced drug availability.

## C. Impaired Drug Tolerability and Drug-Induced Disease, Disorder, Dysfunction or Toxicity

In response to chemical substances, drugs, or xenobiotics, drug-induced disease, disorder, dysfunction, or toxicity manifests as cellular damage or organ physiologic dysfunction, with one potentially leading to the other.

Adverse drug reactions can be categorized as 1) mechanism based reactions which are exaggerations of pharmacologic effects and 2) idiosyncratic, unpredictable effects unrelated to the primary pharmacologic action. Although some

side effects appear shortly after administration of a drug, some side effects appear long after drug administration or after cessation of the drug. Furthermore, these reactions can be categorized by reversible or irreversible manifestations of the drug-induced toxicity referring to whether the clinical symptomology subsides or persists upon withdrawal of the offending agent.

In the first category, excessive drug effects may result from alterations of pharmacokinetic parameters by either drug-drug interactions, pathophysiologic disease mediated alterations in the organs or processes involved in absorption, distribution, metabolism, or excretion, or genetic predisposition to heightened pharmacodynamic effect of the drug. The excessive or heightened response may be receptor or drug target or non-receptor or non-drug target mediated.

There are a large number of adverse events that are suspected and or known to occur as a result of administration of a drug, agent, or candidate therapeutic intervention. For example, many antineoplastic agents act by prevention of cell division in dividing cells or promoting cytotoxicity via disruption of DNA synthesis, transcription, and formation of mitotic spindles. These agents, unfortunately, do not distinguish between normal and cancerous cells, e.g. normally dividing cells and cancer cells are equally killed. Therefore, adverse events of antineoplastic agents include bone marrow suppression leading to anemia, leukopenia, and thrombocytopenia; immunosuppression rendering the patient susceptible and vulnerable to infectious agents; and initiation of mutagenesis and the formation of alternate forms of cancer, in many cases, acute myeloid leukemia.

In another example of predictable adverse events related to drug therapy is immunosuppression as a result of therapy to reduce or ablate immune response. This therapy includes but is not exclusive to prevention of graft vs. host or autoimmune disease. These agents, e.g. corticosteroids, cyclosporine, and azathioprine, all suppress humoral or cell-mediated immunity. Patients taking these agents are rendered susceptible to microbial infections, particular opportunistic infections such as cytomegalovirus, pneumocystis carinii, Candida, and sperigillus. Furthermore, long-term immunosuppressive therapy is associated with increased risk of developing lymphoma. Individual drugs are associated with renal injury (cyclosporine) and interstitial pneumonitis (azathioprine).

In the second category of adverse events, idiosyncratic reactions arise often by unpredictable, unknown mechanisms or reactions that evoke immunologic reactions or unanticipated cytotoxicity.

Adverse reactions in this category are often found together, because often it is difficult to ascertain the etiology of the offending reaction. These toxic events can be specific for a target organ, e.g. ototoxicity, nephrotoxicity, hepatotoxicity,

neurotoxicity, etc. or are caused by reactive metabolic intermediates and are toxic or create local damage usually near the site of metabolism.

Immunologic reactions to drugs are thought or result from the combination of the drug or agent with a protein to form an antigenic protein-drug complex that stimulates the immune system response. Without the formation of a complex, most small molecular drugs are unable, alone, to elicit an immunological response. First exposure to the offending drug produces a latent reaction, subsequent exposures usually results in heightened and rapid immunological response. These allergic reactions, characterized by immunohypersensitivity, are most dramatic in anaphylaxis. There are other immune responses that result in adverse reactions or toxicities they include but are not limited to : 1) immune response mediated cytotoxicity which occurs when the drug-protein complex binds to the surface of a cell and this cell-complex is then recognized by circulating antibodies; 2) serum sickness which occurs when immune complexes of drug and antibody are found in the circulation; and 3) lupus syndromes in which the drug or reactive intermediate interact with nuclear material to stimulate the formation of antinuclear antibodies.

In addition to the immune phenomena described above, there are other drug reactions that are syndromes involving allergic reactions. These reactions include, but are not limited to, skin e rashes, drug induced fever, pulmonary reactions, hepatocellular or cholestatic reactions, interstitial nephritis, and lymphadenopathy. Further, there are some drug reactions that mimic allergic reactions but are not immune related. For example, such reactions are due to direct release of mediators by drugs and are called anaphylactoid reactions. An example of this type of adverse event is reaction to radiocontrast dye.

These are common adverse drug reactions that may prevent a candidate therapeutic intervention from use, continued development, and marketing rights. Some of these reactions are reversible, others are not.

Adverse drug reactions include, but are not limited to, the following organs systems: a) hemostasis which encompass blood dyscrasias (feature of over half of all drug-related deaths) which are bone marrow aplasia, granulocytopenia, aplastic anemia, leukopenia, pancytopenia, lymphoid hyperplasia, hemolytic anemia, and thrombocytopenia; b) cutaneous which encompass urticaria, macules, papules, angioedema, morbilliform-maculopapular rash, toxic epidermal necrolysis, erythema multiforme, erythema nodosum, contact dermatitis, vesicles, petechiae, exfoliative dermatitis, fixed drug eruptions, and severe skin rash (Stevens-Johnson syndrome); c) cardiovascular which includes arrhythmias, QT prolongation, cardiomyopathy, hypotension, or hypertension; d) renal which includes glomerulonephritis and tubular necrosis; e) pulmonary which includes asthma, acute pneumonitis,

eosinophilic pneumonitis, fibrotic and pleural reactions, and interstitial fibrosis; f) hepatic which includes steatosis, hepatocellular damage and cholestasis; g) systemic which includes anaphylaxis, vasculitis, fever, lupus erythematosus syndrome; and h) the central nervous system which includes tinnitus and dizziness, acute dystonic reactions, parkinsonian syndrome, coma, convulsions, depression and psychosis, and respiratory depression.

In the cases whereby severe, fatal reactions occur after drug administration, there may be a warning label in the product insert.

For example, tricyclic antidepressants can cause central nervous system depression, seizures, respiratory arrest, cardiac arrhythmias and arrest. The mechanism for the injury is a result of the increased synaptic concentrations of biogenic amines and inhibition of postsynaptic receptors.

Acetaminophen can cause hepatic necrosis as a result of prolonged high dose usage or overdose. In the hepatocyte, acetaminophen is converted to a toxic metabolite that binds to glutathione. As the concentration of acetaminophen increases the levels of glutathione are depleted and the toxic acetaminophen metabolite then binds liver macromolecules. Aggregation of polymorphonuclear neutrophils in hepatic microcirculation may cause ischemia and foster necrotic events.

Halothane can cause hepatic necrosis as well as prodrome fever and jaundice. Interestingly, the liver effects of halothane are usually after a first time exposure. The hepatic reaction is thought to occur via a genetic predisposition to deranged metabolism with the formation of toxic metabolites.

#### **D. Pharmacokinetic Parameters as Potential Mechanisms of Drug-Induced Adverse Reactions Leading to Disease, Disorder, Dysfunction or Toxicities**

##### **1. Absorption**

Absorption is the pharmacokinetic parameter that describes the rate and extent of the drug, agent, or candidate therapeutic intervention leaves the site of administration. Although absorption is critical for the drug, agent, or candidate therapeutic intervention to ultimately reach the site of physiologic action, the term bioavailability is the parameter that is clinically relevant. Bioavailability is the term used to define the extent to which the active component of the drug, agent, or candidate therapeutic intervention reaches the its site of physiologic action or a biological fluid to which has access to the site of biological action. Although bioavailability is related to all pharmacokinetic parameters, e.g. absorption, distribution, metabolism, and excretion, bioavailability is primarily dependent on the

first ability of the drug, agent, or candidate therapeutic intervention to be absorbed from the site of delivery, i.e. cross cellular membranes.

There are many factors that influence absorption of a drug, agent, or candidate therapeutic intervention. For example, compound solubility, conditions of absorption, and route of administration. In the present invention, we concern ourselves with genes that are involved in the active or passive process of drug, agent, or candidate therapeutic intervention absorption through a biological membrane.

The absorption surface is dependent on the route of administration. For example, absorption of drugs can occur via 1) oral (enteral); 2) sublingual; 3) injections (parenteral, i.e., intravenous, intramuscular, intraarterial, intrathecal, intraperitoneal, or subcutaneous); 4) rectal; 5) inhalation (pulmonary); 6) topical application (skin and eye). In each of these routes of administration, the adsorption rate and extent is dependent on the concentration of the drug at the site, the patency of the epithelial cells, local biological conditions, and function of the active or passive transport.

Absorption can affect both the efficacy and safety of a drug, agent, or candidate therapeutic intervention. For example, for a compound to achieve full pharmacologic potential, it must be available at the target site, be active, and be unbound. In regards to safety, absorption affects safety in one or more of the following: site of delivery pain, necrosis, or irritation; rate of administration; and erratic available concentrations.

## 2. Distribution

The distribution of the drug, agent, or candidate therapeutic intervention is dependent on the rate and extent the compound enters the bloodstream. Once in the bloodstream, the compound may be distributed to the interstitial and cellular fluids. The distribution of drugs to target tissues can be categorized into two phases. The first distribution phase, is dependent on cardiac output and regional blood flow, both of which are dependent on the health and status of the cardiovascular system. In a second distribution phase, diffusion into tissues is dependent on the level and extent that the drug, agent, or candidate therapeutic intervention is bound. Drug binding by proteins found in the blood can serve to protect the compound from modifications by enzymes, proteins, or compounds in the circulation and or limit the bioavailability of the compound to enter target tissues or individual cells.

Drug entry into tissues requires free drug, and drug binding proteins may limit this active or passive transport. Once distributed into tissues, the drug may be

sequestered within that tissue, to render full pharmacologic activity or to prevent that drug from reaching the appropriate target tissue.

Distribution can affect both the efficacy and safety of a drug, agent, or candidate therapeutic intervention. For example, for a compound to achieve full pharmacologic potential, it must be available at the target site, be active, and be unbound. In regards to safety, distribution affects safety in one or more of the following: distribution to a tissue that is more or less affected by the pharmacologic action of the compound, erratic available concentrations, and tissue specific distribution characteristics.

### 3. Metabolism

Drugs or xenobiotics, are usually found in the circulation bound to plasma proteins, generally but not exclusive to serum albumin. It is the bound form of the drug that is taken up by the hepatocyte. Bile salts in the circulation are taken up via organic anion transporters. Once inside the hepatocyte, the drug or bile salt is a substrate for a series of reactions that are either oxidative or reductive or reactions that are conjugative steps in the metabolism of the substrate. Generally these chemical modifications are a refined process to render the substrate more hydrophilic, or polar, to be more likely excreted in the bile (via the intestinal tract) or urine (via the kidneys). However, there are exceptions whereby the redox reactions produce reactive intermediates or products that retard elimination. Except for their role in detoxification, there is little in common among the enzymes involved in the redox detoxification reactions. For certain enzymes there are specific groups that will act as substrates, for others there are general classes of chemical compounds that will be suitable substrates for a given enzyme or enzymes.

In the mammalian liver these mechanisms to detoxify and/or enhance the excretion of metabolic by-products, endogenous substrates, and exogenous molecules. The ability to determine whether hepatic function is inadequate is based upon clinical observation, e.g., the presence of jaundice, right upper quadrant abdominal discomfort or pain, pruritis, or by clinical laboratory analyses, e.g., aspartate transaminase (AST or SGOT) or alanine transferase (ALT or SGPT). The hepatic metabolic and excretory mechanisms are critical for short- and long-term survival and are inheritable characteristics. These hepatic biotransformations mechanisms have broad substrate specificity that have been evolutionarily inherited for the host protection from environmental, biological, and chemical substances.

There are two categories of drug, agent, or candidate therapeutic intervention biotransformation (metabolism). In the first, phase I, functionalization reactions occur. Phase I reactions introduce or expose a functional group to the parent



compound. In general, phase I reactions render the parent compound pharmacologically inactive, however there are examples of phase I reaction activation or retention of activity. In phase II reactions, biosynthetic reactions occur. Phase II conjugation reactions leads to a covalent linkage between a functional group on the parent compound with glucuronic acid, sulfate, glutathione, amino acids, or acetate. The metabolic conversion of drugs is the liver, however, all tissues have enzymatic activity.

Factors affecting drug biotransformation are 1) induction of metabolizing enzymes, 2) inhibition of enzymatic reactions, and 3) genetic polymorphisms. It is the interplay of these factors and the health and well being of the patient or subject that determines the fate of parent drug molecules in the body.

The first factor affecting drug biotransformation is induction of metabolizing enzyme activity. The metabolic processes that modify drugs or chemicals (oxidation, reduction, or conjugation) can be induced to significant enzymatic activity. Under physiological conditions, the induction process is in place to coordinately metabolize excess substrates. The induction process can be both at the level of enzymatic activity and increased protein levels of the pertinent enzyme or enzymes. Induction may include one or several of the enzymatic pathways or processes in response to the presence of drugs, xenobiotics, endogenous substrates, or metabolic by-products. There may or may not be increased toxicity as a result of increased concentrations of metabolites. Further, induction of phase I reactive processes (oxidation or reduction reactions) may or may not induce the phase II reactive processes (conjugation reactions).

The second factor affecting drug biotransformation is the inhibition of metabolic enzymes. Enzymatic inhibition can occur via 1) competition of two or more substrates for the enzymatic active site, 2) suicide inhibitors, or 3) depletion of required cofactors for the enzymatic pathways or processes in phase I or phase II reactions.

In competitive inhibition, two or more drugs, xenobiotics, or substrates present can interact with the active site of the enzyme. If one drug binds specifically to the enzymatic active site or to an other intracellular regulatory protein molecule, other compounds are blocked from binding and remain unbound. In this case, unmetabolized parent drug or xenobiotic remains in the circulation, potentially for extended periods of time. Competitive inhibition is dependent on the relative specificity of the substrates for the enzymatic active site and the concentration of the drugs or substrates. An example of competitive drug biotransformation inhibition are cimetidine and ketoconazole which inhibit oxidative drug metabolism by forming a tight complex with the heme iron complex of cytochrome P450, and

macrolide antibiotics such as erythromycin and troleandomycin are metabolized to products bind to heme groups on the cytochrome P450 molecules.

In the second case, the inhibition of enzymes involved in the drug biotransformation process may also occur by suicide inactivation. In these cases, the drug or xenobiotic may interact and covalently modify or render inactive the enzyme involved in the metabolic pathway. In this way, the parent drug compound or molecule is not metabolized, nor is it free to interact with another molecule. Examples of suicide inactivators are secobarbital and synthetic steroids (norethindrone or ethinyl estradiol) which bind to cytochrome P450 and destroy the heme portion of the enzyme unit.

In the third case, inhibition of the enzymes involved in the drug biotransformation pathway can also occur by agents or compounds or physiological status that deplete NADPH or other cofactors required for the enzymatic reactions to occur. In the cases of phase I oxidation or reduction, lack of oxygen or NADPH, may reduce the efficiency and activity of a particular enzyme. In phase II reactions, cofactors provide specific groups for the enzymatic covalent modification of the drug or xenobiotic. These phase II cofactors are required for conjugation biotransformation reactions to occur and depletion of these cofactors would be rate limiting.

The third factor that can affect drug biotransformation is genetic polymorphism. Differences among individuals to metabolize drugs have long been known. Observed phenotypic differences, as determined by amount of drug excreted, through polymorphically controlled pathway/s has lead to a generalized classification of slow (poor) metabolizers and fast (rapid or extensive) metabolizers. In general, poor metabolizers are those with impaired metabolism of a drug via a polymorphic pathway have been associated with an increased incidence of adverse effects. In addition, to date all major deficiencies in drug metabolizing activity are inherited as autosomal recessive traits. Fast or rapid metabolizers are those individuals with processes that extensively metabolize a drug via a polymorphic pathway. The fast or rapid metabolizers have been associated with an increased incidence of ineffective treatment. In these individuals active drug is rapidly metabolized to less active or inactive metabolites such that a reassessment of the pharmacokinetic parameters and dosing regimen may require analysis or readjustment, respectively, for appropriate therapy to occur.

The first observed and catalogued genetic polymorphism associated with drug metabolism was described for isoniazid. Isoniazid is a primary drug prescribed for the chemotherapy of tuberculosis. Marked interindividual variation in the elimination of this drug was observed and genetic studies of families revealed that

this variation was genetically controlled. Isoniazid is predominantly metabolized via N-acetylation. In the analysis of the phenotypically distinct individuals, it was shown that slow acetylators were homozygous for a recessive gene and fast acetylators were homozygous or heterozygous for the wild type gene. It has been  
5 determined that the incidence of the slow acetylator phenotype is approximately 50% for U.S. caucasians and blacks, 60-70% of Northern Europeans, and 5-10% in Asians. Other drugs have been shown to be polymorphically acetylated, e.g. sulfonamides (sulfadiazine, sulfamethazine, sulfapyridine, sulfameridine, and sulfadoxine), aminogluthethimide, amonafide, amrinone, dapsone, dipyrone,  
10 endralazine, hydralazine, prizidilol, and procainamide. Other drugs that first undergo metabolism and then polymorphically acetylated are clonazepam and caffeine.

Another common genetic polymorphism associated with oxidative metabolism is exemplified by the drug debrisoquine (a sympatholytic  
15 antihypertensive). It was discovered that variable inter-patient hypotensive response was due to differing metabolic rates of debrisoquine 4-hydroxylase. Further analysis of family studies revealed that oxidative metabolic reactions are under monogenic control. A cytochrome P450 enzyme, CYP2D6, was determined to be the target gene for debrisoquine 4-hydroxylase activity. Poor metabolizers of desbrisoquine  
20 are homozygous for a recessive CYP2D6 allele and rapid or fast metabolizers are homozygous or heterozygous for the wild type CYP2D6 allele. Urinary metabolic ratio can be determined after administration of a probe drug and phenotypic assignments (poor or extensive metabolizer) can be identified. The extent of debrisoquine metabolic analysis achieved clinical importance as it was determined  
25 that other drugs were poorly metabolized in individuals that poorly metabolized debrisoquine. For example, anti-arrythmics such as flecainide, propafenone, and mexiletine; antidepressants such as amitryptiline, clomipramine, desipramine, fluoxetine, imipramine, maprotiline, mianserin, paroxetine, and nortriptyline; neuroleptics such as haloperidol, perphenazine, and thioridazine; antianginals such  
30 as perhexilene; opioids such as dextromethorphan and codeine; and amphetamines such as methylenedioxymethamphetamine. Further, many  $\beta$ -adrenergic antagonists are metabolized and are subject to polymorphic influence in elimination patterns.

Another example of a genetic polymorphism affecting oxidative metabolism was described for mephenytoin, a drug prescribed for epilepsy. It was shown that a  
35 deficiency in the 4'-hydroxylation of S-mephenytoin is inherited as an autosomal recessive trait. The other main metabolic pathway, N-methylation of R-mephenytoin to 5-phenyl-5-ethylhydantoin remains unaffected. Individuals with poor metabolic rate of mephenytoin are subject to adverse central effects, i.e.

sedation. Other drugs can be grouped into the poor mephenytoin metabolizers are mephobarbital, hexobarbital, side-chain oxidization of propranolol, the demethylation of imipramine, and the metabolism of diazepam and desmethyldiazepam. Further analysis of other drugs such as the metabolism of antidepressant drugs (citalopram), the proton pump inhibitor omeprazol, the antimalarial drugs pantoprazole and lansoprazole cosegregate with mephenytoin metabolites.

Because the majority of metabolic enzymes for the conduct of drug biotransformation occurs in the liver, impairment of liver function as a result of hepatic pathological conditions or other disease states can lead to alterations of hepatic or other organ metabolic drug biotransformation. Liver disease pathologies such as hepatitis, alcoholic liver disease, fatty liver disease, biliary cirrhosis, and hepatocarcinomas can impair function of normal physiological metabolic pathways. Further, decreases in hepatic circulation as a result of cardiac insufficiency, hypertension, vascular obstruction, or vascular insult can affect the rate and extent of drug biotransformation. For example drugs with a high hepatocyte extraction ratio would have different metabolism rates affected by alterations of hepatic circulation. Changes in liver blood flow can affect the rate and extent of the metabolism and the clearance of the parent drug. In all cases of hepatic pathological conditions, the affect on drug biotransformation and clearance of parent drugs or metabolized products will be dependent on the severity and extent of the liver organ and hepatocellular damage.

Although hepatic damage may affect the metabolism and clearance of a parent drug or metabolic by-product, residual concentrations of parent drug or metabolic by-products may be deleterious to the liver and its metabolic functions. Following nonparenteral (enteral) administration of a drug, a significant portion of the drug will be metabolized by intestinal or hepatic enzymes before it reaches the general circulation. This first pass effect may generate active drug (administered drug was a prodrug), inactive drug, or toxic drug. Prior to circulation of the metabolized product, circulation to the kidney, the major organ for excretion of the hydrophilic moiety, and excretion via the urine will occur. Therefore, a metabolic product of hepatic metabolic pathways can affect the liver, kidney, and other organs of the body prior to excretion.

#### a. Phase I Drug Biotransformation: Oxidation and Reduction Reactions

##### *Enzymatic Oxidation of Drugs*

In oxidative metabolism, oxidases catalyze the transfer of electrons from substrate to oxygen, generating either hydrogen peroxide or superoxide anions. There are two oxidases present in hepatocytes; they are aldehyde oxidases and

monoamine oxidases. Both of these enzymes have broad substrate specificity and contribute broadly to the metabolism of drugs. A third oxidase, xanthine oxidase, may contribute to the oxidation of drugs, due its ability to catalyze the oxidation of heterocyclic aromatic amines, for example methotrexate and 6-mercaptopurine.

5 Xanthine oxidase in intact tissues is present as a NAD-dependent dehydrogenase, and is converted to an oxidase when there is disruption of the tissue, for example during hepatic cellular damage.

Aldehyde oxidase catalyzes the oxidation of fatty aldehydes to carboxylic acids and the hydroxylation of substituted pyridines, pyrimidines, purines, and pteridines. Generally, xenobiotic aromatic nitrogen heterocycles are metabolized by this enzyme.

10 Monoamine oxidase is present in two forms, A and B. They are dimeric proteins consisting of identical subunits and FAD is covalently linked to the protein through a cysteinyl residue. Catalytic cycles of monoamine oxidases A or B occur in discrete steps that take an amine and convert it to an aldehyde, while in the process creating hydrogen peroxide and ammonia. These oxidases have a broad specificity; they protect mitochondrial proteins from xenobiotic amines and hydrazines. Further neurotransmitters are metabolized through this route, e.g. serotonin, dopamine, and catecholamines. Primary alkylamines containing

15 unsubstituted methylene group or groups adjacent to the nitrogen exhibits activity. Activity increases as the length of a side chain, with optimal side length being C6. These enzymes also catalyze the oxidation of secondary and tertiary amines and acyclic amines. Hydrazines can be oxidized by these oxidases. Substrates for monoamine oxidases include but are not exclusive to the following amines:

20 benzylamine, dopamine, tyramine, epinephrine, N-methylbenzylamine, and N,N-dimethylbenzylamine; and the following hydrazines: procarbazine 1,2-dimethylhydrazine.

Mono-oxygenases are present in liver cell homogenates and contain two distinct types of xenobiotic mono-oxygenases. They are the cytochrome P450 and the flavin-dependent mono-oxygenases.

30 The liver microsomal P-450 system consists of a flavoprotein, and a family of related, but distinct, hemoproteins. The flavoprotein catalyzes the transfer of the electrons from NADPH to the hemoprotein, and is the mono-oxygenase. The reaction also requires phosphatidylcholine. The reductase is a monomeric flavoprotein that contains both FAD and FMN. The reductase is specific for

35 NADPH as a reductant, but other oxidants can be substituted. In addition to cytochrome P-450, the flavoprotein catalyzes reduction of quinones, nitro, and azo compounds.

There are many P450 gene families. Subsequent cloning and sequence determination has afforded the ability to divide this gene family into three main groups, CYP1, CYP2, and CYP3, that are responsible for the majority of drug biotransformation. There are further subdivisions in each of these families, examples being CYP2D6, CYP3A4, CYP2E1, as well as others.

Examples of enzymatic inductive processes that affect biotransformation reactions involve the P450 gene family. Specifically, glucocorticoids and anticonvulsants induce CYP3A4; isoniazid, acetone, and chronic ethanol consumption for CYP2E1. Many inducers of the cytochrome P450 enzymes also induce conjugation metabolic enzymes, e.g. glucuronosyltransferases.

In contrast to the monooxygenases, multiple forms of the terminal oxidase (P-450) are present in the hepatocyte. There are many distinct isoforms characterized in different species including humans. It should be noted that mitochondrial P-450 exhibit little or no activity in the metabolism of drugs, xenobiotics, biological compounds, or chemicals. Representative functional groups oxidated by the microsomal P-450 system are as follows: alkanes (hexane, decane, hexadecane); alkenes (vinyl chloride, aflatoxin-B1, dieldrin); aromatic hydrocarbons (naphthylene, bromobenzene, benzo(a)pyrene, biphenyl); aliphatic amines (aminopyrine, benzphetamine, ethylmorphine); heterocyclic amines (3-acetylpyridine, 4,4'-bipyridine, quinoline); amides (N-acetylamino fluorene, urethane); ethers (indemethacin, pheancetin, p-nitroanisole); and sulfides (chlorpromazine, thioanisole).

There are many P450s that have been identified in human liver. Substrate specificities vary among these P-450 dependent mono-oxygenases. For example, P4501A1 prefers polycyclic aromatic hydrocarbons; P-4501A2 prefers arylamines, arylamides; P-450A26 prefers coumarin, 7-ethoxycoumarin; P-450 2C8, 2C9, 2C10 prefers tolbutamide, hexobarbital; P-450 2C18 prefers mephenytoin; P-450 mp-1, mp-2 prefers debrisoquine and related amines; P450 2E1 prefers ethanol, N-nitrosoalkylamines, vinyl monomers; P-450 3A3, 3A4, 3A5, 3A7 prefers dihydropyridines, cyclosporin, lovastatin, aflatoxins.

The effect of genetic polymorphism of the P450s has been known for some time. For example, debrisoquine and related drugs; alfentanil, tolbutamide; (S)mephenytoin. Because the P450s can be induced by xenobiotics, an enhanced metabolic rate or efficiency can lead to one drug affecting the potency, efficacy, dosing of another. For example, women taking rifampicin or barbiturates can lead to metabolic inactivation of synthetic oral contraceptives.

The flavin-containing mono-oxygenases are the principle enzymes catalyzing the N-oxidation of tertiary amine drugs to N-oxides. The N-oxides are found in

abundance in serum. Although isoforms have been identified and the catalytic cycle is similar to the cytochrome P450 system, flavin-containing mono-oxygenases substrate specificity differs. Unlike the other flavin-bearing mono-oxygenases, these flavin-containing mono-oxygenases are present in the cell as very reactive oxygen-activated form. It is believed that particular protein structure stabilizes the nucleophilic molecule. Since the molecule is so highly reactive, precise substrate-to-enzyme fit is unnecessary. The following lists substrate types and examples oxidized by the flavin-containing mono-oxygenases: tertiary amines (trifluoperazine, bromopheniramine, morphine, nicotine, pargyline); secondary amines (desipramine, methamphetamine, propanolol); hydrazines (1,1-demethylhydrazine, N-aminopiperidine, 1-methyl-1-phenylhydrazine); thiols and disulfides (dithiothreitol,  $\beta$ -mercaptomethanol, thiophenol); thiocarbamides (thiourea, methimazole, propylthiouracil); sulfides (dimethylsulfide, sulindac sulfide).

Examples of drugs that undergo oxidative reactions are: N-dealkylation (imipramine, diazepam, codeine, erythromycin, morphine, tamoxifen, theophylline); O-dealkylation (codeine, indomethacin, dextromethorphan); aliphatic hydroxylation (tolbutamide, ibuprofen, pentobarbital, meprobamate, cyclosporin, midazolam); aromatic hydroxylation (phenytoin, phenobarbital, propanolol, phenylbutazone, ethinyl estradiol); N-oxidation (chlorpheniramine, dapsone); S-oxidation (cimetidine, chlorpromazine, thioridazine); deamination (diazepam, amphetamine).

#### *b. Enzymatic Reduction of Drugs*

The reductases are a class of enzymes that are involved in the metabolic reduction of xenobiotics. This class of enzymes includes the aldehyde and ketone reductases, the quinone reductases, the nitro and nitroso reductases, the azoreductases, the N-oxide reductases, and the sulfoxide reductases. These classes of enzymes are involved in sequential one-electron reduction of some functional groups and produce radicals that can produce damage cellular components directly or indirectly.

The dehydrogenases consist of alcohol dehydrogenases, aldehyde dehydrogenases, or dihydrodiol dehydrogenases. This class of enzymes is involved in the catalysis of hydrogen transfer to a hydrogen acceptor, usually a pyridine nucleotide.

#### *c. Hydrolysis of Drugs*

Alternative reactions of detoxification and metabolism of drugs and xenobiotics are initial steps of hydrolysis. Esters, amides, imides, or other

functional groups that are generated as a result of a hydrolysis reaction can alter the hydrophilicity of a molecule and enhance urinary excretion. Hydrolysis occurs both enzymatically and nonenzymatically. Hydrolysis of proteins before they are degraded has been suggested as a step in the process of the aging of intracellular proteins. Antibodies with an affinity for certain esters and certain proteases e.g. 3-phosphoglyceraldehyde dehydrogenase and carbonic anhydrase, have been shown to have esterase activity.

Enzymatic hydrolysis of drugs and xenobiotics include the following enzymes: esterases, amidases, imidases, and epoxide hydratases. Examples of drugs undergoing hydrolysis reactions are: procaine, aspirin, clofibrate, lidocaine, procainamide, indomethacin.

Other hydrolytic processes include reactions owing to both enzymes in tissues, circulation, and those elaborated by microorganisms in the lower bowel; for example, sulfatases, glucuronidases, and phosphatases.

#### b. Phase II Drug Biotransformation: Conjugation Reactions

In addition, to the redox reactions of the hepatocyte to detoxify or metabolize xenobiotics, there are a series of conjugation reactions. The substrates for these reactions are generally the products from the redox reactions described above. These conjugation reactions involve donation of a suitable hydrophilic molecular group to an accepting xenobiotic or its metabolite. The major function of these covalent modifications is to render the parent compound pharmacologically inactive. The covalent addition of such a group to a parent drug or compound not only inactivates the substrate but also renders the recipient molecule more polar and is more readily excreted via the bile ducts into the intestinal tract or via the urine.

Lipophilic compounds that have one of the functional groups that can serve as an acceptor undergo enzymatic catalysis with a second, donor substrate. The conjugation reactions include the following broad categories: glucuronidation, sulfation, methylation, N-acetylation, and conjugation with amino acids. The enzymes involved in these reactions are as follows: UDP-glucuronyltransferase, alcohol sulfotransferase, amine N-sulfotransferase, phenol sulfotransferase, glutathione transferase, catechol O-methyltransferase, amine N-methyltransferase, histamine N-methyltransferase, thiol S-methyltransferase, benzoyl-CoA glycine acyltransferase, acetyltransacetylase, cysteine S-conjugate N-acetyltransferase, cysteine S-conjugate N-acetyltransferase, cysteine conjugate  $\beta$ -lyase, thioltransferase, and rhodanese. Each of these enzymes has donor and acceptor specificities. The importance of these reactions in the detoxification and metabolism of drugs and xenobiotics are discussed in the examples



Examples of drugs that are known to be conjugated are: glucuronidation (acetaminophen, morphine, diazepam); sulfation (acetaminophen, steroids, methyldopa); acetylation (sulfonamides, isoniazid, dapsone, clonazepam).

#### 5 4. Excretion

Excretion of parent drugs and metabolites can occur in the excretory organs, namely the kidneys, liver, lungs, skin, and breasts (milk). The kidneys are the most important organs for the excretion of drugs and metabolites. Renal excretion involves glomerular filtration, active tubular absorption, and passive tubule  
10 reabsorption. The more hydrophilic the compound is the more readily excreted via urine. In addition, many drugs and metabolites are excreted via the bile into the intestinal tract. These metabolites may be excreted in the feces, or may be reabsorbed by the gastrointestinal epithelial cell lining. Organic anions and cations, steroids, fatty acids, and other drugs may be specifically transported into the bile  
15 canniculus.

In all of the metabolism and excretion routes, the physiologic goal is to detoxify and rid the body of drugs, xenobiotics, endogenous or exogenous chemicals, or compounds that may or may not be deleterious to the major organs of the body. In principle the detoxification mechanisms function to attain this goal,  
20 however there are many cases of major organ toxicity upon exposure to drugs or metabolites of drugs. Although drugs and drug metabolites predominantly affect the liver and kidneys due to the circulatory and physiological processes, other organs can be affected. In the present invention, we address specific genes that may have polymorphic sites affecting metabolic rates to ultimately affect these major organ  
25 functions.

##### a. Excretion of Drugs and Drug Metabolites via the Bile

After parent drugs or xenobiotics are metabolized by redox and or conjugation reactions, the modified products can then be actively transported into  
30 the bile cannicula. The transport occurs in an energy dependent fashion requiring ATP. It has been shown that the transporters involved in the active transport from the basolateral (sinusoidal) to the apical (canalicular) surfaces of hepatocytes are members of the ATP binding cassette (ABC) family. The transmembrane electrical potential required to maintain the chemical and electrical potentials required for this  
35 active transport is provided by the  $\text{Na}^+/\text{K}^+$  ATPases located on the basolateral membrane. Other ion transporters are the potassium channel, sodium-bicarbonate symporter, chloride-bicarbonate anion exchanger, and the chloride channel. In the cholangiocyte there are other ion transporters, for example chloride-bicarbonate

anion exchanger, isoform 2, and other organic-solute transporters. Bile acids, phosphatidyl choline, organic anions, organic cations, and cholesterol are actively transported. Approximately 5% of the transporters is multi-drug resistance protein 1 (MDR1) and the remaining are the phospholipid transporter multi-drug resistance protein 3 (MDR3), alicular multispecific organic- anion transporter (multi-drug resistance associated protein (MRP2 or cMOAT), canalicular bile-salt-export pump (BSEP or SPGP(sister of p-glycoprotein)), sodium-taurocholate cotransporter, organic anion-transporting polypeptide, glutathione transporter, and a chloride-bicarbonate anion exchanger are also involved in the transport.

These transporters have been identified to move specific molecules or compounds across biological membranes. For example, the MDR1 protein mediates the canicular excretion of bulky lipophilic cations, e.g. anticancer drugs, calcium channel blockers, cyclosporine A, and various other drugs. In contrast, the MDR3 protein transports phosphatidyl choline from the inner leaflet to the outer leaflet of the canicular membrane. Phosphatidyl choline then can be selectively extracted by intracanicular bile salts and secreted into bile as vesicles or mixed micelles. MRP2 is involved in the transport of amphipathic anionic substrates e.g. leukotriene C4, glutathione-S conjugates, glucuronides (bilirubin diglucuronide and estradiol-17 $\beta$ -glucuronide), sulfate conjugates, and is responsible for the generation of bile flow independent of bile salts within the bile cannicula. SPGP is the canicular bile salt export pump in the mammalian liver.

The hepatocyte has the ability to recruit the ATP-requiring transporters when faced with excessive metabolites. After synthesis, these transporters are stored in compartments that, in response to cAMP, can be actively moved through the cell to the membrane and fused to the cannicula. The active movement from the intracellular compartment to the membrane requires microtubules, cytoplasmic kinesin, cytoplasmic dynein, and calcium. It has been shown that peptides activate phosphoinositide 3 kinase, and increased turnover of phosphoinositides drives the formation of 3'-phosphoinositol, which can activate the transporter in the membrane and ultimately increases movement to the cannicular membrane. Signaling pathways via the activation of rab5 stimulate the active movement of the transporters to the internal compartment.

#### b. Excretion of Drugs and Drug Metabolites via the Kidney

Excretion of drugs or drug metabolites via the kidney and into the urine involves three processes: 1) glomerular filtration, 2) active tubular secretion, and 3) passive tubular reabsorption. The amount of drug or metabolites entering the tubular lumen is dependent on its fractional plasma protein binding and glomerular filtration

rate. In the proximal renal tubule anions and cations are actively transported by carrier mediated tubular secretion and bases are transported by a separate system that secretes choline, histamine, and other endogenous bases. In the proximal and distal tubules there is passive reabsorption of these molecules. The concentration gradient for back-diffusion is created by sodium and other inorganic ions and water.

#### **E. Inflammatory or Immunological Disease, Disorders, or Dysfunctions**

Inflammatory or immunological diseases and clinical symptoms includes diseases and processes such as: arthritis (including rheumatoid arthritis, osteoarthritis, and other degenerative syndromes of the joints), asthma, chronic obstructive pulmonary disease (including bronchitis, bronchiectasis, emphysema and other pulmonary diseases associated with obstruction to air flow), interstitial or restrictive lung diseases, autoimmune disease (including systemic lupus erythematosus, scleroderma and other diseases characterized by autoantibodies), transplantation (often treated with long term immunosuppressive therapy), pain associated with inflammation, psoriasis and other inflammatory skin diseases, atherosclerosis (for which there is strong data supporting the role of inflammatory pathogenetic mechanisms), and hepatitis, among other diseases. One skilled in the art will recognize that there may be overlap between some of the conditions listed.

Challenges in treating diseases with a significant inflammatory or immunological component include: (i) limited understanding of the pathophysiologic basis of these diseases and conditions, , (ii) a complex mix of immune/inflammatory mediators operating simultaneously, with the primary (initiating) events often unclear and the relative importance of different mediators unknown, (iii) medical interventions that rarely produce specific effects, or address the underlying pathophysiologic basis of the disease or condition. Thus, medical management of inflammatory or immunologic disorders is empirical in nature, is associated with multiple undesirable side effects, and disease progression is common. Based upon these clinical realities and the difficulties drug developers face in developing new treatments for diseases with an inflammatory or immunologic component, the use of genotypebased stratification to identify populations enriched for responders, nonresponders, and/or those likely to develop undesirable side effects will provide clear commercial and medical benefits. Ultimately medical practitioners and patients will also benefit from an enlarged choice of medicines with superior safety and efficacy when used in conjunction with genetic diagnostic tests.

Inflammation is a complex process that comprises different cellular and physiologic events that can be initiated by tissue injury, by abnormal immune

function, or by a wide variety of other endogenous or exogenous factors, not all of which are understood. The inflammatory process can also escape normal regulatory control and become part of the disease process.

Autoimmunity is one aspect of some diseases associated with abnormal immunologic function. Such diseases are characterized by the presence of autoantibodies and oligoclonal B cell populations. Immunological reactions associated with loss of self tolerance may be localized to a specific tissue, or may be systemic. Ultimately, in severe cases, the immune system produces life threatening damage to tissues, physiological function is compromised. Autoimmunity can be initiated by a variety of endogenous (genetic predisposition and others) and exogenous (chemicals, drugs, microorganisms, and others) factors.

#### **F. Endocrine and Metabolic Diseases**

The treatment of endocrine and metabolic diseases presents a challenge to physicians and other medical practitioners because the available therapeutics are only partially effective in only a fraction of patients (e.g. antiobesity medications). Further, many currently used medicines produce serious adverse effects (e.g. long term corticosteroid therapy). Therapeutic benefits and toxic side effects have to be balanced in each patient. This requires much attention to drug selection, dosage adjustment and monitoring for potential adverse events on the part of patients and care givers. These limitations of therapy are especially true for the most debilitating endocrine and metabolic diseases such as diabetes and obesity

Difficulties in treating endocrine and metabolic diseases are attributable to factors such as limited understanding of disease pathophysiology, lack of specificity of pathophysiologic changes (e.g. different pathophysiologic mechanisms in patients with similar clinical presentation) and lack of specificity of therapeutic compounds. Further, most medical therapy is directed to the amelioration of symptoms or other secondary changes (e.g. achieving effective control of blood sugar), not the arrest or reversal of underlying pathophysiologic processes. One good example of the difficulty of developing and marketing effective treatments for metabolic and endocrine diseases is the recent history of obesity therapeutics. Only a few products have been approved for treatment of obesity in the United States, and one of them, the anorectic agent dexfenfluramine (d-FF; Redux), a 5-HT reuptake inhibitor and releasing agent, was withdrawn from marketing due to safety problems (pulmonary hypertension, valvular heart disease). Further, a recently marketed antiobesity product (sibutramine; Meridia) with a similar mechanism of action Sibutramine, an inhibitor of serotonin and noradrenaline uptake, reduces appetite (inhibition of serotonin and noradrenaline uptake, reducing appetite) is used by only a small

fraction of eligible obese patients because anti-obesity drugs now have a reputation among caregivers and patients as unsafe. Thus approved drugs for the treatment of a disorder that affects many million Americans are only moderately commercially successful because their shortcomings are widely recognized.

5 In summary, medical management of endocrine and metabolic diseases is empirical in nature, is only partially effective, and is associated with multiple undesirable side effects. In view of these clinical realities, the use of genetic tests to identify treatment responders, nonresponders, and/or those likely to develop undesirable side effects will have a major impact on use of existing classes of drugs  
10 for treatment of endocrine and metabolic diseases, as well as on the development and use of new drugs to treat these diseases.

### **G.Cardiovascular and Renal Diseases**

15 The treatment of cardiovascular and renal diseases presents a challenge to physicians and other medical practitioners because the available therapeutics are only partially effective in only a fraction of patients. Further, many currently used medicines produce serious adverse effects. Therapeutic benefits and toxic side effects have to be balanced in each patient. This requires much attention to drug selection, dosage adjustment and monitoring for potential adverse events on the part  
20 of care givers – in many cases (e.g. antihypertensive therapeutics) effectively a new pharmacokinetic and pharmacodynamic study must be performed for each patient. These limitations of therapy are especially true of the most debilitating cardiovascular and renal diseases. Although these diseases have distinct clinical presentations, there is extensive overlap in pathogenetic mechanisms and symptoms.

25 Difficulties in treating cardiovascular and renal diseases are attributable to factors such as limited understanding of disease pathophysiology, lack of specificity of pathophysiologic changes (i.e. variation in pathophysiologic mechanisms in patients with similar clinical presentation) and lack of specificity of therapeutic compounds. Further, most medical therapy is directed to the amelioration of  
30 symptoms, not the arrest or reversal of underlying pathophysiologic processes.

In summary, medical management of cardiovascular and renal diseases is empirical in nature, is only partially effective, and is associated with multiple undesirable side effects. In view of these clinical realities, the use of genetic tests to identify treatment responders, nonresponders, and/or those likely to develop  
35 undesirable side effects will have a major impact on use of existing classes of cardiovascular and renal drugs, as well as on the development and use of new drugs to treat diseases of the cardiovascular and renal systems.

## H. Neoplastic Diseases

The unifying feature of neoplastic disease is uncontrolled proliferation and the bulk of modern chemotherapy targets the rapid growth of cancerous tissue. Effective cancer management must destroy or retard the growth of cancerous tissue and prevent the spread of cancerous cells to secondary locations while sparing normal tissues. Cancer therapy has remarkable parallels to the treatment of parasitic infection in that the causative agent is capable of overwhelming growth and rapid mutation to resistant forms. Cancers can differ greatly in their response to chemotherapy: tumors that proliferate rapidly including melanomas, leukemias, and myelomas tend to respond well to classical chemotherapy using cytotoxic agents; tumors that grow slowly, in contrast, such as lung and colon carcinomas tend to respond poorly; the growth of endocrine tumors such as ones of pancreatic, prostate, testicular, ovarian, adrenal, pituitary, or breast origin can be hormonally dependent and treatment with agonists of insulin, estrogen, progesterone, testosterone, etc. function can prove valuable; and solid tumors are more apt to respond to treatment with antiangiogenesis agents than fluid tumors. Surgery (for solid tumors) and radiation treatment exist as therapies that are often used in conjunction with chemotherapeutic agents. A clinician must select a therapy (often a combination of agents and including radiation treatment or surgery) based on tumor type in addition to evaluating the possible toxicities associated with proposed therapeutic regimens, taking the patients current hepatic, renal and myeloproliferative function into account. Since current practice utilizes high doses of cytotoxic agents to minimize the formation of metastases as well as the appearance of secondary, resistant neoplasms, avoiding toxicity becomes a serious issue given the narrow therapeutic index of most drugs in this category.

Medical management of neoplastic disease is empirical in nature, is associated with severe undesirable side effects, and disease progression is common. Based upon these clinical realities and the difficulties medical practitioners face in therapy of neoplastic disease, drug development based upon genotype to identify responders, nonresponders, and or those likely to develop undesirable side effects will be an undeniable beneficial addition to current medical practice.

## II. Identification of interpatient variation in response; identification of genes and variances relevant to drug action; development of diagnostic tests; and use of variance status to determine treatment

Development of therapeutics in man follows a course from compound

discovery and analysis in a laboratory (preclinical development) to testing the candidate therapeutic intervention in human subjects (clinical development). The preclinical development of candidate therapeutic interventions for use in the treatment of human diseases, disorders, or conditions begins at the discovery stage  
5 whereby a candidate therapy is tested *in vitro* to achieve a desired biochemical alteration of a biochemical or physiological event. If successful, the candidate is generally tested in animals to determine toxicity, adsorption, distribution, metabolism and excretion in a living species. Occasionally, there are available animal models that mimic human diseases, disorders, and conditions in which  
10 testing the candidate therapeutic intervention can provide supportive data to warrant proceeding to test the compound in humans. It is widely recognized that preclinical data is imperfect in predicting response to a compound in man. Both safety and efficacy have to ultimately be demonstrated in humans. Therefore, given economic constraints, and considering the complexities of human clinical trials, any technical  
15 advance that increases the likelihood of successfully developing and registering a compound, or getting new indications for a compound, or marketing a compound successfully against competing compounds or treatment regimens, will find immediate use. Indeed, there has been much written about the potential of pharmacogenetics to change the practice of medicine. In this application we provide  
20 descriptions of the methods one skilled in the art would use to advance compounds through clinical trials using genetic stratification as a tool to circumvent some of the difficulties typically encountered in clinical development, such as poor efficacy or toxicity. We also provide specific genes, variation in which may account for interpatient variation in treatment response, and further we provide specific  
25 exemplary variances in those genes that may account for variation in treatment response.

The study of sequence variation in genes that mediate and modulate the action of drugs may provide advances at virtually all stages of drug development. For example, identification of amino acid variances in a drug target during  
30 preclinical development would allow development of non-allele selective agents. During early clinical development, knowledge of variation in a gene related to drug action could be used to design a clinical trial parameters in which the variances are taken account of by, for example, including secondary endpoints that incorporate an analysis of response rates in genetic subgroups. In later stages of clinical  
35 development the goal might be to first establish retrospectively whether a particular problem, such as liver toxicity, can be understood in terms of genetic subgroups, and thereby controlled using a genetic test to screen patients. Thus genetic analysis of drug response can aid successful development of therapeutic products at any stage of

clinical development. Even after a compound has achieved regulatory approval its commercialization can be aided by the methods of this invention, for example by allowing identification of genetically defined responder subgroups in new indications (for which approval in the entire disease population could not be achieved) or by providing the basis for a marketing campaign that highlights the superior efficacy and/or safety of a compound coupled with a genetic test to identify preferential responders. Thus the methods of this invention will provide medical, economic and marketing advantages for products, and over the longer term increase therapeutic alternatives for patients.

There are some examples whereby there is no direct evidence that a gene or genes are involved in drug response of a candidate therapeutic intervention. In these cases, however, there is genetic data supporting a role of a variance or variances involved in the etiology, progression, or risk of the neurologic or psychiatric disease. These cases, including but not limited to anxiety, Huntington's disease, demyelinating disease, pain, Parkinson's disease, spasticity, and stroke are described below with details of current therapies and potential genetic involvement of variances in drug responses.

#### Neurological and Psychiatric Diseases

There are some examples whereby there is no direct evidence that a gene or genes are involved in drug response of a candidate therapeutic intervention for the treatment of neurological or psychiatric disease. In these cases, however, there is genetic data supporting a role of a variance or variances involved in the etiology, progression, or risk of the neurologic or psychiatric disease. These cases, including but not limited to anxiety, Huntington's disease, demyelinating disease, pain, Parkinson's disease, spasticity, and stroke are described below with details of current therapies and potential genetic involvement of variances in drug responses.

#### A. Anxiety

##### Description of Anxiety

Anxiety is a common, nonspecific symptom associated to a greater or lesser degree with many psychiatric diseases, including psychoses, neuroses, mood disorders and personality disorders. It is also an inevitable component of everyday life brought on by stressful events such as medical or surgical procedures. Some prominent nonspecific symptoms of anxiety include tachycardia, chest pains, or irregular heartbeat; epigastric distress; headache, dizziness, syncope, or paresthesias. It is usually some combination of these physical manifestations of anxiety that impels patients to seek medical care. It has been estimated that approximately 13% of primary care visits are substantially attributable to anxiety.



There are both acute and chronic anxiety syndromes. The acute forms include panic attacks and event-related anxiety. Chronic, or generalized anxiety is a pervasive feeling of nervousness that does not subside. Because both panic-attack and generalized anxiety lead to desire for being alone or away from public places, many patients adopt agoraphobic tendencies. These patients can become housebound because of fear of having a panic attack in a public setting.

#### Current Therapies for Anxiety

The principal treatments for anxiety have been benzodiazepines, monoamine oxidase inhibitors, antidepressants, and  $\beta$ -adrenergic antagonists. In all cases, both panic attack and generalized anxiety, concurrent continued behavioral and psychological therapy is required to regain a sense of normal life function.

#### Limitations of Current Therapies for Anxiety

The difficulty in determining the efficacy of psychotropic drugs for the treatment of anxiety is the subjective contribution of the nonpharmacologic factors that are associated with anxiety. However, the relative safety of benzodiazepines, pharmacologic actions, and high demand make these products drugs of choice in the treatment of anxiety.

The benzodiazepines are associated with side effects due to CNS depression, drowsiness and ataxia. Other side effects are: increase in hostility or irritability, confusion, weight gain, skin rash, nausea, headache, impairment of sexual function, vertigo, and lightheadedness.

#### Future Drug Development for Anxiety

In Tables 2, 13 and 19, there are listings of candidate genes and specific single nucleotide polymorphisms that may be critical for the identification and stratification of a patient population diagnosed with anxiety based upon genotype. Current pathways that have possible involvement in the therapeutic benefit of anxiety include, but are not limited to, serotonergic, GABAergic, purinergic, adrenergic, glutaminergic, dopaminergic, cholinergic, glycinergic, cholecystokinin, corticotropin releasing factor, histaminergic, opiate, taurine, oxytocin, neuropeptide Y, estrogen, hemostasis, tachykinin, vasopressinergic and second messenger intracellular cascades gene pathways that are listed in Tables 2, 13 and 19. One skilled in the art would be able to identify these pathway specific gene or genes that may be involved in the manifestation of anxiety, are likely candidate targets for novel therapeutic approaches, or are involved in mediating patient population differences in drug response to therapies for anxiety.

Below, Table 26 lists the therapies in development for anxiety categorized by the gene pathway mechanism of action as in Table 7. The listed candidate therapeutic interventions response in patients with anxiety may be affected by polymorphisms in genes as described above.

## B. Huntington's disease

### Description of Huntington's Disease

Huntington's disease (HD) is an inherited disorder characterized by the gradual onset of motor incoordination and cognitive decline in mid-life. Symptoms develop insidiously either as a movement disorder manifested by brief jerk-like movements of the extremities, trunk, face, neck (choreas) or as personality changes. Fine motor incoordination and impairment of rapid eye movements are early features. Bradykinesias and dystonia may predominate if the onset occurs early in life.

As the disorder progresses the involuntary movements become more severe and are characterized by: dysarthria, dysphagia, and impaired balance. Cognitive deficits begin by features of slowed mental processing, difficulty in organizing complex tasks, and memory deficits (family, friends, and immediate situation is unaffected). These patients have tendencies to become irritable, anxious, and clinically depressed. In rare cases there may be paranoia or delusional states. There are approximately 25,000 Americans diagnosed with HD.

### Current Therapies of HD

Current therapies do not include alternatives for the treatment of the progression of the neurodegeneration. Medical management of the associated clinical symptoms includes the following categories: depression, psychosis, and choreas. In the cases of depression and psychoses, the therapies of beneficial therapeutic use are described in this invention.

The treatment of choreas generally includes neuroleptic agents that affect dopaminergic pathways by antagonism at the receptor level. Monoamine depleting drugs can also be used to minimize choreas.

### Limitations of Current Therapies of HD

#### Efficacy Limitations

Conventional and atypical neuroleptic agents are not uniformly able to reduce the signs and symptoms of choreas in HD patients. Efficacy varies in the HD population in one or combination of the following ways: 1) patients are only

partially responsive or 2) patients are therapy resistant. Unfortunately, limited efficacy in a HD population in light of the presence of undesirable side effects may lead to compliance issues, aberrant drug abuse behavior, and further safety issues.

Thus, a clinician when presented with a newly diagnosed HD patient, in general, follows standard neurological society or published guidelines for first line therapy. However, when faced with a partially responsive or therapy resistant patient, the clinician can choose from multiple agents, none being completely effective, has limited guidance or rationale to select one agent the other, and follows an empirical medical decision making course of action.

#### Toxicity Limitations

Unfortunately, conventional neuroleptic drugs are uniformly, and atypical are latently, associated with undesirable dose-dependent side effects. These include but are not exclusive to sedation, weight gain, cognitive deficits, sexual or reproductive insufficiencies, agranulocytosis, cardiovascular complications, neuroleptic malignant syndrome (parkinsonism with catatonia), jaundice, blood dyscrasias, skin reactions, epithelial keratopathy, seizures, and extrapyramidal effects. The blood dyscrasias include mild leukocytosis, leukopenia, and eosinophilia. The skin reactions include urticaria and dermatitis and are usually associated with phenothiazines. Epithelial keratopathy and opacities in the cornea is associated with chlorpromazine therapy. In extreme cases these effects may impair vision. These ocular deposits tend to spontaneously disappear upon discontinuation of chlorpromazine drug therapy.

The extrapyramidal side effects of conventional neuroleptics include dystonia (facial grimacing, torticollis, oculogyric crisis), akathisia (feeling of distress or discomfort leading to restlessness or constant movement), and parkinsonian syndrome (rigidity and tremor at rest, flat facial expression). With long term usage of conventional neuroleptic drugs, tardive dyskinesias uniformly appear in HD patients.

Tardive dyskinesia is a syndrome of repetitive, painless, involuntary movements. These abnormal involuntary movements are insuppressible, stereotyped, autonomic movements that cease only during sleep, vary in intensity over time, and are dependent on the level of arousal or emotional distress. The syndrome is characterized by quick choreiform (ticlike) movements of the face, eyelids (blinks or spasms), mouth (grimaces), tongue, extremities, or trunk. These movements may have varying degrees of athetosis (twisting movements) and sustained dystonic postures. Increasing the dose of the conventional neuroleptic

agent can reverse extrapyramidal effects observed in patients. However, increasing the dose ultimately leads to more severe dyskinesias. Antiparkinson agents tend to exacerbate the tardive dyskinesia symptoms and thus are not used clinically.

Because dopaminergic agonists tend to worsen the symptoms and dopaminergic antagonists tend to retard the symptoms of tardive dyskinesias, the optimal alternative is to use a neuroleptic agent that has selective dopaminergic antagonist activity. This alternative therapy would manage both psychosis and dyskinesias.

Often a clinician faces the dilemma of a patient with medically managed choreas, but the dose-related tardive dyskinesias, agranulocytosis, or seizures compels the medical care personnel to opt to switch therapies to possibly those agents or drugs with fewer or less severe side effects but with substandard or limited efficacy. Under these conditions, inability to treat the psychotic or chorea symptoms with the backdrop of irreversible dyskinesias leaves the patient with few alternatives.

### III. *Impact of Genotyping on Drug Development for HD*

There have been reports of polymorphisms in key genes that affect neuroleptic activity in schizophrenic patients. These polymorphisms may be further applicable for neuroleptic response in HD patients. For example, within the dopamine D4 receptor subtype, there are known tandem repeats in exon 3. In a recent study, schizophrenic patients on maintenance doses of chlorpromazine were stratified into two groups, one having 2 tandem base pair repeats and the other having 4 tandem base pair repeats. Thirty-four percent of group one patients and 62% of group two patients had a favorable response to chlorpromazine therapy during acute stage treatments. The presence of homogeneous four 48 base pair repeats in both alleles in exon 3 of the dopamine D4 receptor subtype thus appears to be associated with beneficial chlorpromazine response.

Recently, a study of the serotonin receptor subtype 6, polymorphism (T267T vs. C267T) in a group of patients refractory to clozapine therapy was reported. In this study, it appeared that the T267T genotype patients were more likely to respond to continued therapy than those patients with C267T genotype patients.

A recent report documented a correlation of the serotonin 5HTC2 receptor subtype biallelic polymorphism and neuroleptic efficacy. A significant number of schizophrenic patients homozygous for the allele C2 responded unsatisfactorily to antipsychotic medication as compared to control.

Three polymorphisms in the serotonergic receptors, i.e. 5HT2A (T102C); 5HT2C (cys23ser); and 5HT2A (his452tyr) have reports of positive or negative correlation with efficacy of antipsychotic therapies. This disparity in the literature

will, in the future, be further examined in schizophrenic patient populations and correlation may be discovered.

*V. Description of Mechanism of Action Hypotheses for Future Drug Development*

5       The genetic basis of the disease has been identified. A gene, huntingtin, whose protein has a mechanism yet to be defined, has a series of CAG tandem repeats. The number of CAG repeats do correlate somewhat with age of onset and the severity of the disease. Cell death starts in the caudate nucleus by an unknown mechanism. The huntingtin protein is essential to life. The huntingtin protein  
10       undergoes cleavage as cells age. The mechanism of cleavage is performed in part by members of the caspase enzymatic family. As the huntingtin protein is cleaved into smaller units, the peptides become toxic, and it has been shown that the smaller fragments tend to migrate into the nuclear compartment. It has been shown that preventing huntingtin cleavage prevents cellular toxicity. Some of the cleaved  
15       huntingin fragments form aggregates which may promote or be a by-product of neuronal cell death.

      The profound loss of neurons in the brains of patients with HD has lead to many development programs for the promotion of neural regeneration. These programs broadly include cytokines, growth factors, and agents that promote neural  
20       or glial cell growth. Further, consideration of preventing neuronal cell death includes apoptosis inhibition and others. Other programs include prevention of prolonged excitatory neurotransmission. These neurons switch their aerobic metabolism to anaerobic metabolism leading to glycolytic metabolism and excessive production of lactate and metabolic by-products. Excitatory neural inhibition,  
25       improvement of energy metabolism, and inhibition of cell death signals may ultimately play a critical role in preventing, retarding, or halting neurodegeneration in HD patients.

      Further, there may be genes within pathways that are either involved in metabolism of neurotransmitters or are involved in metabolism of various drugs or  
30       compounds. In Tables 1-6, 12-17, 18-23, there are listings of candidate genes and specific single nucleotide polymorphisms that may be critical for the identification and stratification of a patient population diagnosed with HD based upon genotype. Current pathways that may have involvement in the therapeutic benefit of HD include glutaminergic, serotonergic, dopaminergic, cholinergic, opiates, estrogen,  
35       mitochondrial maintenance, growth, differentiation, and apoptosis. secretion gene pathways that are listed in Tables 2, 7, 13, and 19. One skilled in the art would be able to identify these pathway specific gene or genes that may be involved in the manifestation of HD, are likely candidate targets for novel therapeutic approaches,

or are involved in mediating patient population differences in drug response to therapies for HD.

Below in 30 is a list of therapies in development for HD categorized by the gene pathway mechanism of action. The listed candidate therapeutic interventions response in patients with HD may be affected by polymorphisms in genes as described above.

### C. The Demyelinating Diseases

#### Description of Demyelinating disease

Primary demyelinating diseases result in loss of the myelin sheath that surrounds axons, with preservation of the axons. The main demyelinating diseases are multiple sclerosis, including its variants (Marburg and Balo variants of MS and neuromyelitis optica), and the perivenous encephalitides, which include acute disseminated encephalomyelitis and acute necrotizing hemorrhagic leukoencephalitis..

Due to the paucity of information concerning etiology of these diseases, identification and classification is largely descriptive. The most common and best studied of these diseases is multiple sclerosis.

#### Description of Multiple Sclerosis

Clinically, MS usually starts as a relapsing illness with episodes of neurological dysfunction lasting several weeks, followed by substantial or complete improvement. This is the relapsing-remitting phase of the disease. Many patients remain in this stage of the disease for years or even decades, while others rapidly progress to the next stage, secondary progressive MS, in which, with repeated relapses, recovery becomes less and less complete. There is also a steadily progressive relapse-independent form of the disease termed primary progressive MS. This form is characterized by a steady worsening of neurological function without any recovery or improvement, and more often affects men.

#### Current Therapies for Multiple Sclerosis

Although the pathogenesis of MS is not understood, there is accumulating evidence that immunoregulatory mechanisms are involved. Current therapy of MS is therefore directed to modulating immune function and thereby halting or retarding myelin degeneration, or facilitating remyelination. Remyelination has been shown to occur spontaneously in response to therapeutic interventions in animals (both normals and MS models). However, in MS animal models remyelination appears to be aborted soon after it begins.

For relapsing-remitting MS the following agents are currently in use : 1) interferon beta-1 $\beta$  (Betaseron) reduces annual relapse rate and reduces development and progression of new lesions in relapsing-remitting MS as monitored by magnetic resonance imaging (MRI), and has been shown to reduce annual relapse rate, reduce disability progression, and delay increase of lesion volume by MRI in secondary progressive MS; 2) Interferon beta-1 $\alpha$  (IFN-beta-1 $\alpha$ ; Avonex) treatment results in reduced disability progression, annual relapse rate, and new brain lesions, as visualized by MRI; 3) Glatiramer acetate (Copaxone; Copolymer-1; Cop-1) reduces annual relapse rate; 4) Intravenous immunoglobulin, reduces annual relapse rate, and delays disability progression; 5) High-dose methylprednisolone therapy is effective in shortening MS attacks, and may be useful in the long term treatment of secondary-progressive MS; 6) Other agents that have been used with success are mitoxantrone, azathioprine and methotrexate. The latter drug, in particular, has been shown effective in reducing disease activity, both by decreasing the number of exacerbations and by slowing clinical progression. The first four agents are of comparable efficacy in the treatment of relapsing-remitting MS. Not enough trials have been performed to reliably assess the utility of treating nonresponders to one of these treatments with a different treatment, or to assess potential markers of response.

### *III. Limitations of Current Therapies for Multiple Sclerosis*

The available treatments have both efficacy and toxicity limitations. Further, the cost for one year of interferon treatment is approximately \$11,000 and parenteral administration is inconvenient.

#### Partial Response to Therapy

Current therapies reduce, but do not arrest, disease progression, and only a fraction of patients benefit from treatment; approximately 30% of patients on interferons experience reductions in relapse rates. For primary progressive MS, there are currently no effective therapies available; interferon beta-1b has in fact been shown to worsen spasticity in primary progressive MS.

#### Undesired Side-Effects or Toxicities as a Therapeutic Limitation

All interferons are associated to varying degrees with flu-like symptoms, muscle-ache, fever, chills, and asthenia. There are also side effects that are difficult to distinguish from the course of the demyelinating illness, for example interferons may lower the seizure threshold and exacerbate depressive illnesses, two clinical problems also observed in patients without interferon therapy.

### Impact of Pharmacogenomics on Drug Development for Multiple Sclerosis

Aspects of therapy for demyelinating disease that can be addressed by pharmacogenetic methods include: 1) Which patients are most likely to respond to medication? 2) Which drugs are most likely to benefit which patients? 3) What is the optimal dose and duration of treatment? 4) What is the relationship between disease type, stage and manifestations and drug response? 5) Can adverse treatment responses be predicted? As an alternative to directly correlating genetic variants with clinical responses to therapy, one could also use quantitative biochemical, immunological or anatomical measures of disease activity to assess the impact of genetic variation in candidate genes on response to medication. While it is unlikely that all therapeutic responses are under strong genetic control, it is expected that if stratification based upon genotype were performed in clinical trials a correlation between drug response and genotype will be detected for at least some treatment responses. Described below and in Tables 2 and 7 are gene pathways that affect current drug therapy as well as drugs currently in development for MS. Described in the Detailed Description are methods for the identification of candidate genes and gene pathways, patient stratification, clinical trial design and statistical analysis and genotyping for testing the impact of genetic variation on treatment response in multiple sclerosis and other demyelinating diseases.

A sample of therapies approved or in development for preventing or treating the progression of symptoms of MS currently known in the art is shown in Table 32. In this table, the candidate therapeutics were sorted and listed by mechanism of action. Further, the product name, the pharmacologic mechanism of action, chemical name (if specified), and the indication is listed as well.

### Mechanism of Action Hypotheses for Novel Therapies for Multiple Sclerosis: Utility of Genotyping

Several possible mechanisms by which intravenous immune globulin (IVIG) modulates the course of the disease are related to limiting the inflammatory process and repairing the damage by enhancing remyelination. The efficacy of dexamethasone (DX) and methylprednisolone (MP) at high (HD) and low (LD) dose in acute multiple sclerosis (MS) relapses was evaluated by a double-blind trial in 31 patients followed for 1 year. DX and HDMP were similarly efficacious in promoting recovery, while LDMP was ineffective in the short-term outcome and was followed by an early clinical reactivation. The different outcomes seem to be related to different immunomodulating effects, mainly on cerebrospinal fluid (CSF) IgG



synthesis and on peripheral blood and CSF CD4+ lymphocyte subsets. The efficacy of interferon should be investigated in relation to other treatment options, such as immunoglobulin, copolymer I, azathioprine and methotrexate. Other promising therapeutic options (mitoxantrone, intravenous immunoglobulins, drug associations) are under evaluation.

### Pathogenesis of MS

There are three current theories for the cause of MS that have been studied to effectively understand the mechanism of disease as well as establish rationale for the development of effective candidate therapeutic interventions. The three current theories are 1) viral infection, 2) genetic predisposition, 3) inflammation and autoimmunity, and 4) ion channel modulators.

### Viral Infection

Indirect evidence that there is a single unique virus causing MS is the unusual geographic distribution of the disease. There is a documented north-south gradient of disease prevalence, migration studies, and reports of clustering of cases have indicated an environmental influence on disease susceptibility. Despite years of intense research including viral isolation studies from tissue samples of MS patients and controls, has not resulted in identification of an MS specific virus or viral sequence.

One virus implicated in the pathogenesis of MS is the human herpes virus type 6 (HHV-6). HHV-6 is a neurotropic virus that can establish a latent infection in man. HHV-6 protein and DNA have been isolated and identified from neuroglial cells in active MS spinal lesions. Further, HHV-6 IgM titers in MS patients and HHV-6 DNA identified in serum samples indicate a recent infection. However, to date there is no evidence that HHV-6 is the causal infectious agent of MS. Instead, a hypothesis of molecular mimicry has been proposed as a likely possibility to explain the indirect immune-mediated injury to otherwise normal tissue in the course of clearing an infectious agent. Besides HHV-6, there are other neuro-specific infectious agents that may damage the CNS through this mechanism. The molecular similarity (mimicry) between virus and myelin antigens may be permissive for immunological cross-reactivity between HHV-6 and myelin antigens. In this model, the T-cells become activated, cross the blood brain barrier and misidentify normal myelin antigens as 'virus' resulting in T-cell mediated cellular and tissue injury.

### Genetic Susceptibility to MS

Although MS is a sporadic disease, studies have pointed to an organized familial clustering, which suggests a genetic predisposition to MS. Equally likely, these studies also suggest that there is a genetic predisposition to an environmental stress or causal event.

The most convincing evidence of a genetic predisposition to MS is derived from studies of a population-based study of twins. The risk of MS increases with the degree of shared information within a family. There is further a marked increase in concordance for MS in the comparison of monozygotic and dizygotic twins.

### Inflammation and Autoimmunity in MS

While it is clear there is an inflammatory component to the lesions of MS, is it currently unclear whether the immune system plays a role in initiation of the characteristic damage of white matter.

In experimental studies of animal models of MS, there appears to be T-cell, CD4+ and CD+8, autoreactivity to several putative CNS antigens including myelin basic protein, proteolipid protein, myelin oligodendroglial glycoprotein, 2',3'-cyclic nucleotide phosphodiesterases, myelin-associated glycoproteins, and viral antigens. Further, there appears to be down regulation of cytokine production including TNF- $\alpha$  and IL-3.

These observations have led to the following proposed mechanism of immune-mediated injury in an MS lesion. Genetic and environmental factors (e.g. viral infection, molecular mimicry, bacterial lipopolysaccharides, superantigens, local metabolic stress, oncogene expression, or reactive metabolites) may potentiate the movement of T-cells through the blood-brain barrier to the CNS. These same genetic and environmental factors may act within the CNS to upregulate the expression of intracellular adhesion molecules on endothelial cells and the circulating T-cells which in turn enhances the rolling, binding, diapedesis, and ultimate migration of the T-cells into the CNS. The same genetic and environmental factors may activate the secretion of  $\alpha\beta$ -crystallin on the oligodendrocytes rendering these cells more susceptible to T cell recognition. The T-cells once in the CNS then secrete cytokines (TNF- $\beta$  and INF- $\gamma$ ) activate the antigen presenting cells (astrocytes, microglia, and macrophages) enhancing (macrophage, microglia) or inhibiting (astrocytes) further immune signaling. The activated T cell then encounters the putative MS antigen or antigens in light of the MHC class II molecules on the antigen presenting cells, resulting in T-cell activation. The activated T-cells can then differentiated into Th1 or Th2 type CD4+ cells which then results in proinflammatory or anti-inflammatory cytokine signaling, respectively. It

has been shown in MS patients that antibody, complement, and antibody-mediated cellular toxicity mechanisms may cause the myelin lesions.

#### Ion Channel Modulations in MS

Reduction of the depolarization in postsynaptic membranes by modulation of the ion channels in nerve and muscle tissue has been postulated as a mechanism to ablate aberrant neurotransmission in demyelinating neurological disease. Proposed gene targets to produce the membrane depolarization are the nicotinic acetylcholine receptor, voltage gated Na<sup>+</sup> channels, and other ion channels.

#### Future Therapeutic Strategies for MS

The future strategies for the beneficial therapy of MS are borne out of the existing mechanisms of the etiology of this demyelinating disease as previously described. They are antivirals, cytokine and anticytokine strategies, immune deviation strategies to enhance Th2 cell/cytokine performance, matrix metalloproteinase inhibitors, trimolecular complex strategies, cathepsin B inhibitors, and oxygen radical scavengers.

Specifically, antivirals include valcyclovir and acyclovir. Cytokine and anticytokine strategies include TNF inhibitors, antiinflammatory cytokines, and inhibitors of proinflammatory cytokines. Immune-deviation strategies to enhance Th2 cell/cytokine predominance includes pentoxifylline, transforming growth factor- $\beta$  (TGF- $\beta$ ), and Il-10, Il-4 alone in combination with corticosteroids. Matrix metalloproteinase inhibitors include D-penicillamine, and hydroxymatate. Trimolecular complex strategies include anti-MHC monoclonal antibodies, MHC class II hypervariable peptide vaccines, anti-T cell monoclonal antibodies, altered peptide ligands, T cell vaccination strategies (myelin basic protein reactive T-cell, T-cell receptor peptide vaccination), co-stimulation strategies (antiB7-1, CTLA-4Ig fusion proteins, CD40/CD40 ligand interactions), and adhesion molecule signaling strategies (monoclonal antibodies, or small molecules directed to these adhesion molecules).

Neural regeneration development programs will include growth factors including NGF, BDGF, CNTF, NT-3, and other cytokines, as well as other factors that are involved in the support of nerve cell viability, growth, and sustaining neural transmission.

Technological advances that reduce difficulties in determining progression of the demyelination by neuroimaging techniques will aid development of new therapies. Estimation of expected clinical and surrogate measures and patterns to

identify, screen, and develop statistically derived stopping rules for efficacy and futility.

Further, there may be genes within pathways that are either involved in metabolism of neurotransmitters or are involved in metabolism of various drugs or compounds. In Tables 2, 13, 19 there are listings of candidate genes and specific single nucleotide polymorphisms that may be critical for the identification and stratification of a patient population diagnosed with MS based upon genotype. Current pathways that may have involvement in the therapeutic benefit of epilepsy include glutaminergic, GABAergic, opiates, corticotropin releasing hormone, potassium channel, prostaglandin, platelet activating factor, cytokines, clot formation, second messenger cascade, growth, differentiation, and apoptosis, cytoskeleton, adhesion, and myelination gene pathways that are listed in Tables 2, 7, 13, and 19. One skilled in the art would be able to identify these pathway specific gene or genes that may be involved in the manifestation of MS, are likely candidate targets for novel therapeutic approaches, or are involved in mediating patient population differences in drug response to therapies for MS.

#### D. Pain

##### Description of Pain

Chronic pain can be caused by chronic pathologic processes in somatic structures or viscera, or by prolonged dysfunction of parts the peripheral or central nervous system.. In all there are approximately 70 million Americans that experience chronic pain. Chronic pain may be the result of recurrent headache, arthritis, back or spinal injuries, musculoskeletal disorders, cardiac or visceral pathologies. Chronic pain is also part of the clinical manifestation of cancer; many of these cases are medically intractable pain. Chronic pain syndromes include polyarteritis nodosa; systemic lupus erythmatosus; entrapment neuropathy; lumbar plexitis; Bell's palsy; carpal tunnel syndrome. Chronic pain can also result from peripheral neuropathies: diabetic neuropathy (neuropathic complications of diabetes mellitus include distal symmetric, sensory, autonomic, asymmetric proximal, cranial and other mononeuropathies); cervical radiculopathy; Guillain-Barre syndrome; brachial plexitis; familial amyloid neuropathy; HIV neuropathy; post spinal cord injury; and post herpetic neuralgia.

##### Current therapies for Pain

Therapeutic management of chronic pain includes a three step ladder approach: non-opioid analgesics are stepwise prescribed in combination with moderate to potent opiates. The guidelines call for a determination by the patient

and the physician of pain relief. Broadly speaking, the guidelines are as follows: mild pain is treated with non-opioid analgesics, moderate or persisting pain is treated with a weak opioid plus non-opioid analgesics, and severe pain that persists or increases is treated with a potent opioid plus non-opioid analgesics.

5 Pain management regimens include not only the use of opioids and non-opioid analgesics, but also benzodiazepines, local anesthetics, anticonvulsants, anticholinergics, serotonin norepinephrine reuptake inhibitors, neuroleptics, and barbiturates. These drugs in combination can relieve associated symptoms of chronic pain syndromes such as anxiety, acute on top of chronic pain, seizures, dry  
10 mouth, delirium, and inability to sleep, respectively.

Treatment options for chronic pain fall into the following categories: 1) general health promotion and relief from exacerbating factors; 2) nonnarcotic pharmacologic; 3) physical; 4) surgical; and 5) narcotic.

15 The nonnarcotic empirical therapies include tricyclic antidepressants (amitriptyline, nortriptyline, doxepin, imipramine), anticonvulsants (carbamazepine, phenytoin); GABAergic agonists (BACLOFEN<sup>®</sup>) and antipsychotics (fluphenazine). Narcotic therapies include opioid agonists (methadone and fentanyl). Devices and surgical therapies can be used in combination with drug therapy. In general these therapies have been shown to reduce pain and each are described in detail below.

20 Antidepressants: The tertiary amines are the most commonly used anti-depressants to manage pain associated with post-SCI. Although the exact mechanism is unknown, the interference with the re-uptake of neurotransmitters (dopamine, norepinephrine, and serotonin) may reduce pain transmission in the afferent  
25 pathways. Further, the increased quantities of these neurotransmitters in the areas of the hyperexcitable neurons, descending pain inhibitory pathways that terminate in the substantia gelatinosa of the dorsal horn, may act to reduce pain transmission. Interestingly, the dose of the tricyclics for the management of pain is approximately half that required for the management of depression. These compounds can be  
30 determined to be effective for pain management in approximately two weeks.

Anticonvulsants: Reports exist describing chronic neuropathic pain syndromes as a central neurophysiologic epileptiform activity of the uncontrolled hyperactive  
35 neurons leading to a convulsive syndrome in the spinal cord. Thus, anticonvulsant therapies are considered to stabilize the threshold against hyperexcitability of neurons and inhibiting the spread of epileptiform activity in neurons involved in nociception. Further, activation of inhibitory neurons may lead to a pain reduction.

Although the data is not conclusive, it appears that anticonvulsants are more effective when given in combination with antidepressants.

5     Neuroleptics: The neuroleptics are thought to exert a potentiation of the antidepressants and may impart a dopaminergic antagonism. Neuroleptics are usually given in combination with an antidepressant.

10     GABAergic agonists: Baclofen, a GABAergic agonist when delivered intrathecally was effective in reducing chronic pain in those patients in which the pain was of musculoskeletal origin (83% of these patients), but was ineffective in those patients with neurogenic pain (78% experienced no change).

15     Physical treatments: Physical treatments include transcutaneous electrical nerve stimulation (TENS) and spinal cord stimulation devices. Using TENS, some success has been reported to reduce peripheral pain. Upon placing the electrodes, peripheral sensory nerve stimulation is thought to activate pain inhibitory interneurons in the substantia gelatinosa or dorsal root entry zone of the spinal cord. Spinal cord stimulation devices are programmable multichannel systems with electrodes that may be placed percutaneously, these systems do not require  
20     laminectomy. These stimulators have been shown to reduce chronic pain (perceived pain levels requiring intensive therapies: discomforting, distressing, horrible, and excruciating) by 50% long term. The global ratings for quality of life in these patients demonstrated similar long term improvements. The exact mechanism of how spinal cord stimulation results in a reduction of pain is unknown, but it is  
25     thought to occur through an antisympathetic effect. Further, it seems to be effective in cases in which the patient has neuropathic or an ischemic component to the pain. In patients with peripheral neuropathies (postherpetic neuralgia, intercostal neuralgia, causalgic pain, diabetic neuropathy, idiopathic neuropathy) spinal cord stimulation is able to reduce chronic pain in approximately 50% of the patients.

30     Surgical treatment: If conservative pharmacologic approaches have failed to relieve pain, neurosurgery can be considered. Neurosurgical treatments consist of nerve blocks, neuroablative and neuroaugmentative procedures.

35     Nerve blocks: Peripheral, epidural, and sympathetic nerve blocks have been attempted. However, the analgesic effect is usually short-lived and ineffective against central mechanisms of pain.

Neuroablative procedures: There are surgical procedures that are rarely performed because they have been shown to be ineffective, i.e. sympathectomies, neurolyses, dorsal rhizotomies, cordectomies, anterolateral cordectomies, mesencephalotomies, and cingulotomies. These procedures have been superseded by dorsal root entry zone (DREZ) surgery. The surgical procedure involves a laminectomy of the appropriate vertebrae, examination of the DREZ and radiofrequency lesions of the DREZ. The mechanism of this ablative surgery is thought to be due to the destruction of the secondary pain sensory neurons in the substantia gelatinosa in the dorsal horn. Success of this procedure on the reduction of pain has been reported at 60-90%.

Neuroaugmentative procedures- deep brain stimulation: Electrodes are implanted in the periventricular gray matter, specific sensory thalamic nuclei, or the internal capsule.

#### Limitations of Current Therapies of Pain Due to Low Efficacy

The severity of pain can be debilitating and significantly interfere with the productivity and quality of life. Existing therapies for chronic pain are often inadequate and characterized by the tendency to become ineffective with time. Potent opiates are part of an analgesic regimen, however, dose-limiting side effects and antinociceptive capacity, tolerance and potential for dependence limit their widespread use. Surgical intervention is sometimes attempted, but often such procedures are ineffective and at best provide only temporary relief.

There are many syndromes by which the above combination drug therapy is insufficient to relief symptoms of chronic pain. There are common reasons for unrelieved pain associated with the patient or family, i.e. belief that pain in cancer is inevitable and untreatable, failure to contact a physician, patient denial, failure to take medications, noncompliance due to fear of addiction, noncompliance due to a belief that tolerance will rapidly develop and adequate pain relief then will not be available in the advanced stages, and lastly noncompliance due to the adverse side effects. Common reasons for unrelieved pain associated with the physician or nurse are: denial of the patient's pain, unawareness of pain intensity, failure to perceive patient denial, failure to treat pain aggressively, fear of patient addiction, failure to prescribe appropriate doses for analgesia, failure to monitor the patient's progress, failure to understand alternative drug combinations, and finally failure to give psychological support to the patient and family. Despite these common reasons for unrelieved chronic pain, even under positive conditions chronic pain can be intractable in a variety of diseases.

The coexistence of pain and depression in these patients is a dependent relationship, i.e. when the pain is unmanaged the depression becomes more severe, the reverse (increased depression leads to increased pain) relationship is less likely to occur. The characteristic intensity of the pain and psychological impact prompts extreme potential solutions. Some of these pain syndromes are more resistant to analgesic therapy, for example approximately half of the individuals with spinal cord injuries endure chronic pain and 30% experience severe, debilitating chronic pain. Approximately 75% of advanced stage cancer patients experience moderate to severe pain and approximately half of these individuals are refractory to standard therapy for management of pain.

Other efficacy limitations include: slow onset of symptoms (2-3 weeks) before efficacy detection for tricyclic antidepressants.

#### Limitations of Current Therapies of Pain Due to Toxicity or Undesired side effects

In the stepwise approach to therapy, physicians are able to monitor and adjust the doses to limit undesired side effects of opioids: sedation, cognitive impairment, myoclonus, addiction, and respiratory depression. Further, opiate tolerance is a well documented effect seen in routine narcotic users and abusers. These side effects may provoke a use of opioid rotation in a pain management schedule.

Although the use of opioids in acute and chronic cancer associated pain is well accepted, their use in chronic noncancer pain has been widely considered to be inappropriate due to concerns over efficacy, toxicity and addiction.

Other unwanted or undesirable side effects include tardive dyskinesias limit the use of neuroleptics in the management of chronic pain; oral baclofen is associated with drowsiness and confusion. Further, baclofen may cause hepatotoxicity. Complications of radiofrequency lesions of DREZ procedure includes cerebrospinal fluid leaking, loss of sensory/motor functions, exacerbation of bowel, bladder, or sexual dysfunction, and epidural/subcutaneous hematomas. Patients must consider the risks of this procedure, particularly the potential loss of two levels of sensation. Associated with deep brain stimulation are complications due to the release of large amounts of natural opioids leading to deafferentation and nociceptive pain.

#### Impact of Genotyping on Drug Development for Pain

As described above, there is evidence to suggest that there are efficacy and safety differences to drug therapy in the pain patient population. Although not all of these responses may be attributable to genotypic differences, it is expected that if



stratification based upon genotype were performed, a reasonable correlation between drug response and genotype may become obvious. As described below, there are gene pathways that are involved with current drug therapy and those that may be potentially involved in the future. As described in the Detailed Description, methods for the identification of candidate genes and gene pathways, stratification, clinical trial design, and implementation of genotyping for appropriate medical management of a given disease is easily translated for pain syndromes. As described below in section V. below there are likely gene pathways as are those that are outlined in the gene pathway Table 2 and CNS matrix table 7.

For example, optimization of GABAergic, opiate, or ion channel modulation mediated therapy of pain further demonstrates the utility of selection of a potential epilepsy patient that has a predisposing genotype in which selective analgesics or agents are more effective and or are more safe. In considering an optimization protocol, one could potentially predetermine variance or variances within the GABAergic receptor, ion channel or ion channel mediated mechanisms of neurotransmission, or GABAergic receptor mediated intracellular mechanism of action that is preeminently responsible for drug response. By embarking on the previously described gene pathway approach, it is technically feasible to determine the relevant genes within such a targeted drug development program for pain.

A sample of therapies approved or in development for preventing or treating the progression of symptoms of pain currently known in the art is shown in Table 33. In this table, the candidate therapeutics were sorted and listed by mechanism of action. Further, the product name, the pharmacologic mechanism of action, chemical name (if specified), and the indication is listed as well.

#### Description of Mechanism of Action Hypotheses for Future Drug Development for Pain

The persistence of pain most likely involves a cascade of pathological neurochemical events that lead to abnormal sensory hyperexcitability and excitotoxicity. The persistence of hyperexcitability involves a sequence of neuroplastic events in the spinal cord. In particular, the hyperexcitability cascade involves NMDA receptor mediated intracellular calcium-dependent increase of nitric oxide (NO) and cGMP production. These signals facilitate long-term alterations in neuronal excitability and central sensitization. The altered spinal neurochemical environment results in an impairment of neural inhibitory function. In particular, inhibitory gamma-aminobutyric acid (GABA)-ergic interneurons are susceptible to excessive excitatory amino acid release. Recent studies suggest that abnormal pain sensations may be alleviated by application of GABA receptor

agonists. The analgesic capacity of GABA receptor agonists has been demonstrated in numerous animal models of acute and chronic pain.

Further, there may be genes within pathways that are either involved in metabolism of neurotransmitters or are involved in metabolism of various drugs or compounds. In Tables 2, 13, and 19, there are listings of candidate genes and specific single nucleotide polymorphisms that may be critical for the identification and stratification of a patient population diagnosed with pain based upon genotype. Current pathways that may have involvement in the therapeutic benefit of epilepsy include glutaminergic, serotonergic, dopaminergic, adrenergic, cholinergic, histaminergic, purinergic, GABAergic, glycinergic, melatonin, nitric oxide, peptide protein hormone processing, opiates, cholecystokinin, tachykinin, bradykinin, corticotropin releasing hormone, somatostatin, galanin, calcium or sodium channels, prostaglandin, cytokines, growth, differentiation, apoptosis, lipid transport/metabolism pathways that are listed in Tables 2, 7, 13, and 19. One skilled in the art would be able to identify these pathway specific gene or genes that may be involved in the manifestation of pain, are likely candidate targets for novel therapeutic approaches, or are involved in mediating patient population differences in drug response to therapies for pain.

#### E. Parkinson's Disease

##### Description of Parkinson's Disease

Parkinson's disease (PD) is one of the major neurodegenerative disorders of middle and old age. PD is a clinical syndrome that is dominated by four clinical symptoms: tremor at rest, bradykinesia, rigidity, and postural instability. There are secondary clinical signs and symptoms also associated with PD and are a result of the following manifestations: mood and intellectual disorder, oculomotor control, and autonomic and sensory dysfunction. PD can be generally categorized by the clinically predominant parkinsonian feature: 1) those patients having tremor, or 2) those patients having postural instability and or gait difficulty as the predominant clinical parkinsonian manifestation. In those patients with tremor predominant disease, the onset is earlier in life and exhibits a slower progression than those patients with gait difficulties or postural instability. In the latter case, the age of onset is later in life and is more frequently associated with bradykinesias, dementia, and the movement disorder progresses more rapidly. The stages of PD have been described and are referred to as Hoehn and Yahr stages I through V; stage I- signs and symptoms are unilateral, stage II- signs and symptoms are bilateral, stage III- signs and symptoms are bilateral and balance is impaired, stage IV- functionally disabled, and stage V- patient is confined to wheelchair or bed.

Resting tremor and bradykinesias are the hallmarks of PD. Bradykinesias are primarily responsible for the altered clinical presentation for most PD patients: retardation of activities of daily living and generalized slowing down of movements, lack of facial expression (hypomimia or masked facies), staring expression due to  
5 limited ability to blink, impaired swallowing which causes drooling, hypokinetic and hypophonic dysarthria, monotonous speech, micrographia, impaired simultaneous and repetitive movements, difficulty in standing from a chair and turning in bed, shuffling gait with short steps, decreased arm swing and other autonomic movements, start hesitation and sudden freezing of motion. Freezing of motion  
10 manifests as a sudden and often unpredictable inability to move and represents the single most disabling parkinsonian symptoms.

There are several disorders other than PD that manifests with parkinsonian symptoms. For example, acquired or symptomatic parkinsonism is the result of infectious (postencephalitic and slow virus) disease, side effects from drugs  
15 (neuroleptics (antipsychotic and antiemetic drugs), reserpine, tertabenazine, amethyl dopa, lithium, flunarizine, cinnarizine), toxins (MPTP, carbon dioxide, manganese, mercury, cesium, methanol and ethanol), cerebrovascular insult (multi-infarct, hypotensive shock), trauma (pugilistic encephalopathy), and others (parathyroid abnormalities, hypothyroidism, hepatocerebral degeneration, cerebral  
20 tumors, normal pressure hydrocephalus, syringomesencephalia). Parkinsonism can also be the result of hereditary degenerative disease, for example autosomal Lewy body disease, Huntington's disease, Wilson's disease, Hallervorden-Spatz disease, olivopontocerebellar and spinocerebellar degenerations, familial basal ganglia calcification, familial parkinsonism with peripheral neuropathy, and  
25 neuroacanthocytosis. Lastly, parkinsonism can be the result of multiple-system degenerations and include for example progressive supranuclear palsy, Shy-Drager syndrome, striatonigral degeneration, Parkinsonism-dementia-amyotrophic lateral sclerosis complex, corticobasal ganglionic degeneration, Alzheimer's disease, and hemiatrophy-parkinsonism. These non-PD parkinsonism symptoms can be  
30 clinically identified as distinct from PD due to the presence of atypical signs or symptoms of the particular dysfunction or syndrome, absence or paucity of tremor, and poor response to levodopa.

#### Current Therapies for PD

35 Pathophysiologically, idiopathic PD cases are almost uniformly identified by the absence of dopaminergic terminals and depigmentation within the substantia nigra and the presence of Lewy bodies (eosinophilic cytoplasmic inclusions in neurons consisting of aggregates of normal filaments). These abnormalities are

predominantly found in the ventrolateral region of the substantia nigra which is the region that projects to the putamen. It has been estimated that at least 80% of dopaminergic neuronal loss within the substantia nigra and an equal degree of dopamine depletion within the striatum is required before signs and symptoms of PD is clinically observed.

There are currently four categories of drug therapies for the treatment of PD: dopaminergic replacement drugs, dopaminergic agonists, anticholinergic drugs, and monoamine oxidase inhibitors. Other therapies include surgical treatment and implantable devices for control of debilitating essential tremor.

Dopaminergic Replacement Drugs- therapy of PD is aimed at replacing the lost dopamine that has resulted in the loss of dopaminergic neurons in the substantia nigra and other brain regions. L-dopa is a prodrug that can be converted to dopamine within the existing neurons. Generally, L-dopa is beneficial in early PD, because it is effectively metabolized in presynaptic terminals and secreted in an active form. Due to the rapid decarboxylation of L-dopa in the periphery, administration of large doses is required to achieve therapeutic benefit. However, L-dopa is usually administered with carbidopa, an inhibitor of peripheral decarboxylation and thus greater concentrations of L-dopa enters the CNS. The combination of L-dopa and carbidopa reduces by 75% the amount of L-dopa required.

Dopaminergic Agonists- dopaminergic agonists can be administered in the early stages of the disease, examples include pramipexole and permax.

Anticholinergic Drugs- anticholinergic agents are prescribed for the management of tremor or inordinate movements associated with PD, examples include artane, and cogentin. The majority of the anticholinergic therapies for the adjunct treatment of PD are long-acting medications thus relief of symptoms may continue through the night when patients have difficulty turning in their bed, and to rise in the morning.

Monoamine Oxidase Inhibitors- inhibition of the metabolism of dopamine by monoamine oxidase can be achieved to increase the synaptic levels of dopamine. An example is selegiline.

Others- catechol-o-methyl transferase inhibitors may be prescribed for the adjunctive treatment of PD, example is Tasmar. An antiviral, symmetrel, has been used for the relief of tremors, rigidity, and bradykinesia. Some  $\beta$ -adrenergic antagonists have been shown to reduce tremors, example is inderal.

Prior to the advent of levodopa therapy, the most effective means of treating disabling tremors associated with PD were thalamotomy and pallidotomy. These ablative surgical procedures are associated with improved tremor and in certain cases, bradykinesias. Recent advances in neurosurgery, e.g. devices to specifically record from the globus pallidus for enhanced localization, have been employed and there is renewed clinical interest in considering these therapies for the treatment of PD. This therapy has the advantage of single procedure therapeutic intervention of disabling tremors.

Another therapeutic alternative for the treatment of essential tremor, a device for deep brain stimulation, is approved for unilateral implantation in the ventral intermediate nucleus of the thalamus. A programmable, implantable pulse generator is implanted just below the clavicle. The implanted device has been shown to be effective in 20% of the patients, bilateral implantation and stimulation is under investigation.

#### Limitations of Current Therapies for PD

Although there are therapeutic alternatives for the early intervention of PD, there are few alternatives for the later stages and for the side effects that develop after long term therapy. These limitations are discussed below.

#### Limitations of Current Therapies due to Low Efficacy

All anti-Parkinson drugs have two qualities that limit the efficiency of treatment regimens. First, the drugs are relatively short acting. A single administration does not relieve symptoms for the duration of waking hours, and multiple administrations are required. The second is that these drugs are all centrally acting drugs and starting dosage is low and slowly increased. Abrupt withdrawal or reductions of any of these medications can lead to deleterious side effects.

L-dopa therapy of PD has therapeutic benefit in the early stages of the disease. However, as the movement disorder progresses, the dopaminergic terminals are lost and the prodrug is no longer converted to the active form. The therapeutic benefit is then limited to the level and extent of the intact postsynaptic neurons.

Long-term therapy with levodopa is associated with dose dependent side effects including inefficacy, "on-off" phenomena, and dyskinesias. Response fluctuations occur in approximately 80% of the patients. These fluctuations consist of wearing-off phenomena, a gradual loss of effectiveness of levodopa related to the timing of administration of the drug, and the on-off phenomena, which is an abrupt

loss of the effectiveness of levodopa that is not related to the timing of administration.

Dyskinesias, consisting of chorea and dystonia, occur in approximately 40% of patients treated with levodopa. These dyskinesias are most frequently observed when plasma levels of L-dopa are high. For patients with preexisting history of psychiatric illness, anticholinergic therapies are less likely to be administered and further if prescribed are less likely to be effective. Thalamotomy and pallidotomy are two surgical procedures that can only be performed once per side. Thus, refractory cases or cases whereby surgery was not sufficient to alter the essential tremor, additional surgery is unavailable. Deep brain stimulation is only 20% effective, requires extensive follow-up, and is associated with a surgical morbidity of 5%. Animal model studies of growth factors, GDNF, affected sprouting of peripheral neurons and those in the spinal cord. Unregulated neural sprouting can be deleterious to neurological function.

#### Limitation of Current Therapies due to Toxicity or Undesired Side Effects

Limitations due to toxicity or undesired side effects for the above discussed treatments of PD are as described below for each of the treatment strategies.

Dopaminergic replacement drugs- as described above, L-dopa is a prodrug that can be of therapeutic benefit to patients with PD. However there are side effects and toxicities associated with L-dopa therapy, they are choreiform and dystonic dyskinesias and other involuntary movements, adverse mental changes such as paranoid ideation, psychotic episodes, depression, and cognitive impairments (dementia). Dyskinesias associated with levodopa, can be debilitating and as uncomfortable as the rigidity and akinesia of PD.

Reductions or withdrawals of L-dopa therapy have been associated with neuroleptic malignant syndrome (NMS). NMS is an uncommon but life-threatening syndrome characterized by fever or hyperthermia, muscle rigidity, involuntary movements, altered consciousness, autonomic dysfunction, tachycardia, tachypnea, sweating, and hyper- or hypotension.

Dopaminergic agonists- as described above, dopaminergic agonists are useful for the activation of post synaptic dopaminergic receptors. The side effects and toxicities associated with dopaminergic agonists are: abnormal involuntary movements, hallucinations, "on-off" phenomena, dizziness, fainting, visual disturbances, ataxia, insomnia, depression, hypotension, constipation, vertigo, and shortness of breath. It

has been observed clinical laboratory transient elevations of blood sera urea and nitrogen, SGOT, SGPT, GGPT, CPK, alkaline phosphatase, and uric acid.

Anticholinergic drugs- the predominant affect afforded by the anticholinergic drugs is to treat the extrapyramidal effects that develop with long-term dopaminergic therapies. This therapy is thus via the anticholinergic and antihistaminergic effects. However, there are adverse reactions that are associated with anticholinergic therapies, they are tachycardia, paralytic ileus, constipation, dry mouth, toxic psychosis (confusion, disorientation, memory impairment, visual hallucinations, possible exacerbation of preexisting psychiatric symptoms or syndromes, blurred vision, dysuria, and urinary retention.

Monoamine oxidase inhibitors- selective inhibition of monoamine oxidase type B (MAO-B) enzyme activity is a useful adjunctive therapy to increase concentrations of dopamine in regions of the brain. Since MAO-B is predominantly found in the brain, fewer systemic side effects occur. Despite this selectivity, there are side effects that are undesirable, they are exacerbation of L-dopa or other dopamine agonist mediated side effects. For example, dyskinesias are enhanced as well as the others listed above.

MAO-B inhibition can be deleterious if administered with a tricyclic antidepressant. Further, a combination of MAO-B inhibitor and meprobamate (an opioid narcotic) has lead to stupor, muscle rigidity, severe agitation, and hyperthermia. Thus, concomitant administration of these two types of drugs is avoided.

Others- inhibition of COMT as described above is a useful therapeutic alternative to many PD patients. However, there are associated side effects and toxicities associated with this drug family. In some patients there is a clinical liver enzyme elevation that requires monthly monitoring and liver function tests are routinely administered every 6 weeks for the first three months of therapy. Liver impairment can result in the reduction of drug detoxification mechanisms, and clinically as jaundice.

Because COMT and monoamine oxidase are the two predominant metabolizing enzymes for catecholamines, concurrent therapy of a COMT and a non-selective monoamine oxidase inhibitor may result in aberrant neuroexcitotoxicity. However, selective monoamine oxidase inhibitors of MAO-B may be administered together.

Other side effects include dyskinesias, nausea, sleep disorders, dystonia, excessive dreaming, anorexia, muscle cramps, and orthostatic hypotension.

Surgical treatment and implantable devices- both pallidotomy and thalamotomy are routinely considered for the treatment of refractory essential tremor. The extent and level of surgical success is dependent on accurate localization of the globus pallidus or the thalamus. Surgery that includes either of these two methods is a one attempt procedure, too much surrounding brain tissue may be lost in subsequent procedures. A side effect may be loss of cerebral function in surrounding areas that may or not result in clinical relevant or observable disease.

#### Impact of Genotyping on Drug Development for PD

For Parkinson's disease, there is evidence to suggest that there are efficacy and safety differences to drug therapy in the PD patient population. Although not all of these responses may be attributable to genotypic differences, it is expected that if stratification based upon genotype were performed, a reasonable correlation between drug response and genotype may become obvious. As described below, there are gene pathways that are involved with current drug therapy and those that may be potentially involved in the future. As described in the Detailed Description, methods for the identification of candidate genes and gene pathways, stratification, clinical trial design, and implementation of genotyping for appropriate medical management of a given disease is easily translated for PD. As described below in section V. below there are likely gene pathways as are those that are outlined in the gene pathway table 2 and the matrix table 7.

#### Description of Mechanism of Action Hypotheses for Future Drug Development

Motor symptoms of PD result primarily from the degeneration of dopaminergic innervation within the putamen and the caudate nucleus. Further dopaminergic degeneration within the mesocortical and mesolimbic systems may be responsible for the cognitive deficits and neurobehavioral symptoms. Autonomic dysfunction often observed in PD patients may be the result of loss of dopaminergic function in the hypothalamus. Although dopaminergic pathways have been studied extensively in post mortem PD patients loss of neurotransmitter pathways that may be responsible for additional clinical symptomology. For example, loss of noradrenergic innervation in the locus ceruleus may contribute to the sudden and unpredictable freezing of motion and degeneration of cholinergic neurons in cortical areas may lead to observed dementia in PD patients.

There have been recent proposals for the mechanism of selective neuronal cell death and functional loss. The proposed mechanisms involved in the



progressive degeneration of dopaminergic neurons are oxidative stress, mitochondrial dysfunction, excitotoxic damage, cell death. Below each is described, with proposed gene targets.

Oxidative stress: In oxidative stress, generation of reactive oxygen species, part of the normal cellular metabolism, is aberrant and levels exceed the regulated cellular metabolism or scavenging mechanisms. The free radicals are generated by the conversion of superoxide ions to hydrogen peroxide via the enzyme superoxide dismutase and the reaction of hydrogen peroxide with reduced glutathione to produce water under the control of glutathione peroxidase. Since it has been documented a 60% reduction in the available reduced glutathione as well as a increased generation of iron associated with neuromelanin, there is a potential shift in the balance of the capacity to scavenge hydrogen peroxide radicals.

Oxidative stress may also be part of circuitous pathway leading to cell death that is as follows: generated free radicals lead to mitochondrial damage, which leads to neuron excitotoxicity, which leads to increased concentrations of intracellular calcium which increases the generation of free radicals. All four pathways (free radicals, mitochondrial damage, neural excitotoxicity, and increased intracellular calcium) can independently lead to neuron cell death. Neuroprotective agents, antioxidative agents, and those agents having effects of halting, retarding, or preventing progression of neurodegeneration may affect one or more of these pathways leading to therapeutically relevant agents.

Mitochondrial damage: In mitochondrial damage, the evidence is born out of the experiments of the specific neurotoxin, MPTP. MPTP is a protoxin, its active form MPP<sup>+</sup> has been shown to result form its inhibition of mitochondrial respiration at the level of complex I, the complex that controls the transfer of one electron from NADH to co-enzyme Q and the transfer of two protons to the mitochondrial inner space, both are then used to synthesize ATP from ADP. In addition, MPP<sup>+</sup> is thought to increase leakage of electrons at complex I, thereby increasing the generation of superoxide. Since the association of MPTP and the evolution of PD in intravenous drug users, it has been shown that there is a decrease in complex I activity in the substantia nigra in PD patients and is relatively unique to PD than other neurodegenerative disorders.

Excitotoxic damage: In excitotoxic damage, the theory posits there is an excess glutaminergic signal from the neocortex and the subthalamic nucleus to the substantia nigra. The excess signal, by acting at NMDA receptors, changes the

permeability of the neural cells to calcium which leads to aberrant post synaptic membrane potentials, enhanced propensity for depolarization and latent repolarization, and activation of nitric oxide synthase (NOS). Activation of NOS leads to the generation of free oxygen radicals through the peroxynitrite reaction.

5 Since the discovery that output neurons of the subthalamic nucleus provide a glutaminergic excitatory input to the substantia nigra, increased calcium influx into the cells and increased formation of nitric oxide via the activation of NOS, may be particularly harmful in PD due to the defect in mitochondrial complex I (see above). Excitotoxic damage to the substantia nigra, thus potentially stems from the integrity

10 of the substantia nigra and or overactivity of the subthalamic nucleus. Thus, strategies aimed at dual actions of enhancing dopaminergic status (dopamine agonism) in the substantia nigra and reducing subthalamic overactivity (glutaminergic antagonism).

Cell Death: In neural cell death, neurons in the substantia nigra undergo death

15 signals via necrosis and apoptosis. In studies involving double labeling with the TUNEL assay (apoptosis) to determine DNA fragmentation and cyanine dye labeling to determine cell structural detail, it was shown that DNA fragmentation and chromatin condensation occurs in the same nuclei of neurons in substantia nigra in patients with PD. Therefore, it appears that the number of apoptotic nuclei in the

20 substantia nigra in PD is greater than that seen in normal aging, consistent with the 10-fold higher rate of cell loss observed in patients with PD. Thus, antiapoptotic agents or therapies may halt, retard, or prevent the progression of neurodegeneration.

Neuroprotection afforded by growth factors in general or specific to neurons

25 have been considered. Growth factors including but not limited to BDNF, GDNF, bFGF have been studied in preclinical animal models of PD. Furthermore, GDNF has been tested in clinical trials.

Alternative neurotrophic agents are a group of ligand called the immunophilins. These ligands have been shown to have neurite growth promoting

30 and neuroprotective effects. Although these effects were first described from results of experiments of the immunosuppressive agents, cyclosporine and FK-506, nonimmunosuppressive analogues have been generated to have neuroprotective capacity while having none of the immunosuppressive qualities. These low molecular weight ligands may hold promise for the medical management of PD.

Based upon these varying hypotheses as stated above, there are many products in development for PD. Table 34 below lists current therapies that are in development for PD.

## F. Spasticity

### Description of Spasticity

Spasticity is a complication that occurs in patients with diagnosed neurodegenerative diseases or cerebral insults such as multiple sclerosis, cerebral palsy, tetanus, traumatic brain injury, post traumatic spinal cord injury, amyotrophic lateral sclerosis, dystonic syndromes (axial dystonia), and stroke. Together there are approximately 1.8 million individuals with spasticity in the U.S. Spasticity is a term that generally refers to one of a variety of forms of muscle hypertonicity, hyperactive muscle stretch reflexes, exaggerated tendon reflexes, and clonus and flexor spasms. Spasticity is commonly described as an isokinetic movement disorder distinguished by velocity-dependent increase in muscle tone characterized by hyperactive stretch reflexes. Patients with spasticity have impaired voluntary control of skeletal muscles, difficulty relaxing muscles once movement has stopped, difficulty initiating rapid movements, and an inability to regulate controlled movement.

Clinically, there are three types of spasticity 1) mild, characterized by hyperactive reflexes and unsustained myoclonus; 2) moderate, characterized by involuntary, uncontrolled contractions, sustained myoclonus neither of which affects activities of daily living; and 3) marked or severe, characterized by unpredictable, uncontrolled paroxysms of spasm and involuntary clonus; these can throw the patient from a wheelchair and often the patient cannot lie in bed quietly; these patients have difficulties using a wheelchair, and transfers (for example: from bed to chair) are problematic.

Broadly speaking there are two groups of spasticity patients: cerebral origin spasticity (etiologies resulting from congenital or acquired injuries such as trauma (traumatic brain injury), anoxia (cerebral palsy), or stroke); spinal origin spasticity (etiologies include spinal cord injury and multiple sclerosis). Uncontrolled spasticity exacerbates physical disabilities, increases the cost of care, and profoundly impacts the quality of life for the patient and family.

### Current Therapies for Spasticity

Mild to moderate spasticity is medically managed with the available treatments. Little to no data are available with respect to waning of efficacy or

progression of the spasticity to more severe forms. With prolonged marked spasticity, contractures (static muscle shortening due to chronic spasm) may develop so that neither lying nor sitting occurs without undue pressure on bony prominences which lead to chronic pressure sores.

As the severity of the spasticity is a continuum, so are the therapies. Spasticity may not require treatment until it becomes painful, bothersome to the patient, or interferes with the activities of daily living. Existing treatments for spasticity may be categorized as systemic or locally acting.

#### Systemic Oral Medications

These are dantrolene (interferes with the excitation-contraction coupling mechanism by interfering with  $\text{Ca}^{++}$  (dantirum), baclofen ( $\text{GABA}_B$  agonist, lioresal), diazepam ( $\text{GABA}$  agonist, valium), tizanidine hydrochloride ( $\beta_2$ -agonist, zanaflex). Back-up medication is the  $\alpha$ -agonist, clonidine.

#### Locally Acting Treatments

Locally acting treatments include intrathecal baclofen, surgical or chemical rhizotomy, and nerve motor point blocks.

#### Intrathecal baclofen

Oral Baclofen is associated with undesirable side effects, however, Baclofen can be delivered to the subarachnoid space attached to a subcutaneous pump. Intrathecal baclofen is a convenient therapy and this form of drug delivery poses fewer central side effects. Further, intrathecal baclofen has shown to reduce spasticity, improve functional capabilities, and increases functional range of passive movement.

#### Surgical intervention

This category includes rhizotomy, which has been most successful in the treatment of spasticity in children with cerebral palsy. In elderly patients that may have stroke induced spasticity, rhizotomy is uncommon and virtually not considered. Another surgical procedure, tendon lengthening, can be considered in those patients in which the lower extremities are affected. This procedure can be considered in those stroke patients who have developed spasticity.

#### Chemical Rhizotomy

Chemodenervation is performed via injections of phenol (or ethanol) or botulinum toxin. In phenol injections, there is neurolysis of the motor nerve. This nerve block technique is useful for motor neuron associated spasticity, and is generally avoided in cases where sensory and motor neurons are hyperactive. The improvement of spasticity after phenol injections may last for a few weeks to years.

Botulinum toxin (BTX) injection into motor neurons has proven useful in the treatment of spasticity. This potent neurotoxin isolated from *Clostridium botulinum*, acts by binding to receptors at the neuromuscular junctions. The binding to the type A toxin is highly specific. The deactivation of intracellular presynaptic vesicles to release acetylcholine in the synaptic cleft can re-establish normal muscle tone and contractility. Intramuscular delivery of BTX has the advantages of lack of sensory effects, lack of caustic chemicals such as phenol, ability to target specific muscle groups through the use of electromyography, and an ability to weaken muscles in a graded fashion.

#### Limitations of Current Therapies for Spasticity: Efficacy and Toxicity Systemic Local Medications

With the exception of dantrolene (which acts directly on muscle), all of the other oral medications act on the central nervous system and there are unwanted effects from the medications, i.e. drowsiness and confusion. Dantrolene and baclofen may cause hepatotoxicity, and dantrolene may cause weakness in other muscle groups. Further, the systemic treatments are highly nonselective. As listed above, there are some indications that these oral medications are less likely to reduce the spasticity; outcomes of oral medications in the treatment of cerebral origin spasticity are poor as compared to good outcomes in patients with spinal origin spasticity. Often combination regimens are used to attempt to curb the myoclonus.

#### Locally Acting Treatments

**Intrathecal Baclofen-** The limitations of this method of delivery are numerous: pump failure, infection, catheter migration, and the need to refill the reservoir. The half-life for ITB is 4-5 hours, and the pump must be refilled at least every 90 days.

**Chemodenervation** this technique is dependent on the proficiency of the surgeon and the accuracy of motor stimulation electromyography (EMG). Phenol injection close to a sensory nerve can result in causalgia due to injury of the myelin sheath of the sensory nerve.

**BTX-** There are studies that demonstrate a resistance to the toxin, these studies have shown that an antibody titer to the toxin prevents full potency.

#### Impact of Pharmacogenomics on Drug Development for Spasticity

As described above, there is evidence to suggest that there are efficacy and safety differences to drug therapy in the spasticity patient population. Although not all of these responses may be attributable to genotypic differences, it is expected that if stratification based upon genotype were performed, a reasonable correlation between drug response and genotype may become obvious. As described below, there are gene pathways that are involved with current drug therapy and those that

may be potentially involved in the future. As described in the Detailed Description, methods for the identification of candidate genes and gene pathways, stratification, clinical trial design, and implementation of genotyping for appropriate medical management of a given disease is easily translated for spasticity. As described  
5 below in section V. below there are likely gene pathways as are those that are outlined in the gene pathway table, Table 2, and the gene pathway /indication matrix table, Table 7.

Optimization of GABAergic or ion channel modulation mediated therapy of spasticity further demonstrates the utility of selection of a potential spasticity patient  
10 that has a predisposing genotype in which selective antispasticity or agents are more effective and or are more safe. In considering an optimization protocol, one could potentially predetermine variance or variances within the GABAergic receptor, ion channel or ion channel mediated mechanisms of neurotransmission, or GABAergic receptor mediated intracellular mechanism of action that is preeminently responsible  
15 for drug response. By embarking on the previously described gene pathway approach, it is technically feasible to determine the relevant genes within such a targeted drug development program for spasticity.

A sample of therapies approved or in development for preventing or treating the progression of symptoms of spasticity currently known in the art is shown in  
20 Table 36. In this table, the candidate therapeutics were sorted and listed by mechanism of action. Further, the product name, the pharmacologic mechanism of action, chemical name (if specified), and the indication is listed as well.

#### Description of Mechanism of Action Hypotheses for Future Drug Development for Spasticity

25 Although the exact mechanism of neurodegeneration-induced spasticity is unknown, the pathophysiology centers on the inadequate release of the inhibitory neurotransmitter, GABA within the spinal cord. Cerebral damage or localized damage within the spinal cord can influence the descending neurons that normally release GABA. However, the afferent input to the spinal cord from the muscle  
30 spindles is unaffected causing a relative increase of excitatory neurotransmitters, particularly glutamate. The consequence is excessive stimulation of the alpha motor neurons resulting in spasticity. Spasticity arising from cerebral damage may only affect certain modulatory inhibitory signals resulting in a variability of spasticity within each and among patients. Since all muscle groups may not be affected  
35 equally, management may be complicated.

Spastic paresis or spastic dystonia appear to arise from an imbalance of inhibition and excitation occurring at the level of the motor neuron. The most basic

component is the abnormal intraspinal response to sensory input. Since modulation of the local spinal cord activity (peripheral segmental reflex arcs and the anterior horn cells) occurs via the descending pathways, loss of the GABA interneurons can affect the balance of excitation/inhibition and leads to hyperexcitable cells that result in an increase in activity of by the extrafusal muscle fibers.

Further, there may be genes within pathways that are either involved in metabolism of neurotransmitters or are involved in metabolism of various drugs or compounds. In Tables 2, 13, and 19, there are listings of candidate genes and specific single nucleotide polymorphisms that may be critical for the identification and stratification of a patient population diagnosed with spasticity based upon genotype. Current pathways that may have involvement in the therapeutic benefit of epilepsy include glutaminergic, adrenergic, cholinergic, GABAergic, calcium channel, mitochondrial maintenance, adhesion, and myelination gene pathways that are listed in Tables 2, 13, and 19. One skilled in the art would be able to identify these pathway specific gene or genes that may be involved in the manifestation of spasticity, are likely candidate targets for novel therapeutic approaches, or are involved in mediating patient population differences in drug response to therapies for spasticity.

#### G. Ischemic Cerebrovascular Disease

##### Description of Stroke

Ischemic cerebrovascular disease is a result of an imbalance of the oxygen supply and the oxygen demand of brain tissue. Stroke is a series of clinical manifestations of reduction of blood supply to the cerebrovascular bed. The signs and symptoms may be complex and depend on the location and extent of the infarct. Ischemic cerebrovascular disease is divided into thrombotic and hemorrhagic stroke.

##### Thrombotic Strokes

Strokes are the result of reduced blood flow supplied by one or more of the major cerebral arteries. Blockage or reduction of blood volume to these main arteries manifests as identifiable neurological symptoms. For example, occlusion of the middle cerebral artery results in contralateral hemiparesis, expressive aphasia, anosognosia and spatial disorientation, contralateral inferior quadrantanopsia, contralateral hemiparesis, sensory loss, contralateral homonymous hemianopsia, or superior quadrantanopsia. Blockage or reduction of the inner carotid artery, anterior cerebral artery, vertebral or basilar arteries, or the posterior artery can result in similarly clinically distinct neurological symptoms.

Transient ischemic attacks (TIA) are similar to a thrombotic stroke in that neurological deficit lasts for a brief period and is generally treated with potent platelet aggregation inhibitors.

Thrombotic strokes are the result of focal blockage of one or more of the cerebral arteries or branches resulting in neurological signs and symptoms lasting greater than one hour. Artherosclerotic plaques in extracranial or intracranial arteries cause approximately two thirds of thrombotic strokes. Embolization, stenosis, or occlusion of one or more of the cerebral arteries or branches may cause thrombotic strokes. Emboli can be of cardiac origin (e.g. mural thrombi, valvular heart disease, arrhythmias (atrial fibrillation), cardiac myxoma, and paradoxical emboli (venous origin). Focal ischemia may also be the result of inflammation and necrosis of extracranial or intracranial blood vessels, i.e. vasculitides (e.g. primary cerebral arteritis, giant cell vasculitis, infectious vasculitis) or the result of hematologic abnormalities (hemoglobinopathy, hyperviscosity syndrome, hypercoagulable states, protein C or S deficiency, the presence of antiphospholipid antibodies). Strokes may be drug related, for example illicit drugs (cocaine, "crack", amphetamines, lysergic acid, phencyclidine, methylphenidate, sympathomimetics, heroin, and pentazocine), ethanol, and oral contraceptives. Lastly there are other diseases that may predispose an individual to a stroke, for example fibromuscular dysplasia, arterial dissection, homocystinuria, migraine, subarachnoid hemorrhage, vasospasm, emboli of other origin (fat, bone, and air), and moyamoya.

### Hemorrhagic Strokes

Approximately 20% of all strokes are the result of intracranial hemorrhage. Approximately half of these cases are into the subarachnoid space and the other half directly in the cerebral tissue. The acute rise in intracerebral pressure generally results in loss of consciousness and many die of cerebral herniation. Similar to thrombotic strokes, hemorrhagic strokes can be considered diffuse or focal, depending on the extent of the vessel disruption. Causes of spontaneous intracranial hemorrhage include arterial aneurysms (berry aneurysms, fusiform aneurysm, mycotic aneurysm, and aneurysm with vasculitis), cerebrovascular malformations, hypertensive-atherosclerotic hemorrhage, hemorrhage into a brain tumor, systemic bleeding diatheses, hemorrhage with vasculopathies, hemorrhage with intracranial venous infarction. Subarachnoid hemorrhage is caused by rupture of surface arteries (aneurysms, vascular formations, head trauma) with blood limited to the cerebrospinal fluid space between the pial and the arachnoid membranes.



### Current Therapies for Stroke

If a hemorrhagic stroke is clear on the CCT, gradual reduction of systemic BP is achieved by standard vascular dilatation medications. Angiography can be useful to identify the source of the hemorrhage. Surgical management of the hemorrhage may be required.

If an ischemic stroke is identified and focal neurological impairments subside over time, a transient ischemic attack (TIA) is suspected. TIA has a high rate of recurrent stroke within a short time frame. Platelet aggregation inhibition is standard therapy; aspirin or ticlopidine. Ticlopidine is associated with neutropenia and agranulocytosis which may be life threatening. Because of these severe side effects, Ticlopidine is reserved for patients who are intolerant to aspirin therapy.

If angiographic review a clearly defined clot is detected, TIA may be surgically treated with endarterectomy.

For the treatment of thrombotic or embolic strokes, each case is independently assessed for surgical management or anticoagulant therapy. The success of thrombotic therapy, e.g. tissue plasminogen activator (tPA), streptokinase, urokinase, relies on timely reperfusion. The therapeutic window for tPA has been shown to be within three hours of onset of symptoms. Hypothermia has been shown to decrease mortality and improve outcomes. Hyperthermia has been shown to worsen both mortality rates and outcomes.

Significant neurologic improvement has been shown to occur within the first three months after stroke symptoms. A clear focus on intensive rehabilitation during this critical time frame has been shown to enhance the eventual outcome for survivors of stroke.

### Limitations of Current Therapies for Stroke

The single most limiting factor of stroke therapy is the rapid identification of stroke symptoms and urgency of intervention within a short time.

### Limitations of Stroke Therapy Due to Low Efficacy and Deleterious Side Effects

Guidelines for the use of tPA in acute ischemic stroke call for the administration of the thrombolytic agents within the first three hours from the onset of symptoms. After three hours four probable deleterious effects have been proven in animal studies and are as follows: 1) cerebral and extracerebral hemorrhage, 2) reperfusion injury, 3) fragmentation of clots, and 4) reocclusion of reperfused vessels.

In both animal models and in humans, reperfusion therapy must be administered within three hours of symptom onset. After three hours deleterious reperfusion injury may occur. Mortality at three months was 17% in the tPA group and 21% in the placebo group ( $p=0.30$ ). Tissue plasminogen activator (tPA), streptokinase, heparin, and urokinase have specific restrictions: tPA has a 6% rate of cerebral hemorrhage; streptokinase is generally not used for thrombotic strokes because of serious side effects and limited quantifiable efficacy, urokinase is generally delivered near the site of the clot or obstruction. Factors influencing the best medical treatment of ischemic stroke must weigh the benefits and limitations of each of these therapies.

#### Impact of Genotyping on Drug Development for Stroke

As described above, there is evidence to suggest that there are efficacy and safety differences to drug therapy in the stroke patient population. Although not all of these responses may be attributable to genotypic differences, it is expected that if stratification based upon genotype were performed, a reasonable correlation between drug response and genotype may become obvious. As described below, there are gene pathways that are involved with current drug therapy and those that may be potentially involved in the future. As described in the Detailed Description, methods for the identification of candidate genes and gene pathways, stratification, clinical trial design, and implementation of genotyping for appropriate medical management of a given disease is easily translated for stroke patients. As described below in section V. below there are likely gene pathways as are those that are outlined in the gene pathway Table 2 and matrix Table 7.

A sample of therapies approved or in development for preventing or treating the progression of symptoms of stroke currently known in the art is shown in Table 37. In this table, the candidate therapeutics were sorted and listed by mechanism of action. Further, the product name, the pharmacologic mechanism of action, chemical name (if specified), and the indication is listed as well.

#### Mechanism of Action Hypotheses for Novel Therapies for Stroke: Utility of Genotyping

There are two categories of genotyping that provided insight on the selection of candidate genes for polymorphic genotypic studies of drug response. One set of likely candidates come from disease etiology or linkage studies. These data may provide input on the genetic etiology or aberrant mechanisms of strokes. Another set are those genes involved in the biochemical or molecular mechanisms of drugs, agents, or candidate therapeutic interventions.

#### Genes Involved in the Etiology of Stroke

Studies have demonstrated that there is a genetic component to thrombotic stroke. These genetic factors may predispose by an individual to thrombotic stroke by inheriting one or more of the following 1) low threshold for aberrant formation of atherosclerotic plaques in intracranial blood vessels; 2) traits that underlie certain specific etiology of stroke; and 3) a disease, disorder, or pathophysiologic process of the CNS in which there are associated molecular or structural disturbances that predispose individuals to strokes. These genetic influences mediating stroke may be candidates for genotyping assays and directly linked to pharmacogenomic programs.

#### Genes Involved in the Mechanism of Drug Action

There are also the biochemical, or molecular mechanisms of drug or candidate therapeutic action that may affect drug action. As described above there is an urgent need for the discovery and development of therapeutic alternatives for the medical management of strokes in which therapy commences beyond the therapeutic windows of thrombolytics.

Recent research and development programs have included the following pathways: 1) glutamate neurotransmitter pathway has been implicated in aberrant excitatory neurotransmission; 2) inflammation is a mechanism that may lead to profound neural cell loss, 3) carnosine pathway, 4) cell adhesion pathways, 5) oxidative stress pathways, 6) growth factor mediated differentiation and rescue of ischemic tissue, and protein maturation and degradation.

#### Ischemic Penumbra, Site of Infarct-Tissue at Risk

Ischemic penumbra is the tissue immediately adjacent to the infarct zone that is viable and morphologically intact but functionally impaired due to the restricted blood flow. Once the blood flow decreases to a certain threshold, this penumbra tissue can be classified as "misery-perfused" because oxygen consumption is preserved and increased oxygen extraction occurs. Ischemic penumbra is, thus, a dynamic process of impaired perfusion and unstable energy metabolism. Since necrosis naturally follows the continued oxygen deprivation, it has been reported that final cerebral infarct size is infarct zone plus the unrecoverable penumbra.

Functional imaging of the cerebral infarct can detect the penumbra tissue, and in some reports the penumbra tissue can be identified up to 48 hours. There is controversy whether the penumbra tissue can be rescued and what is the appropriate time from symptom onset to rescue by reperfusion. Rescue and time to rescue by reperfusion is dependent on the extent of occlusion and severity of metabolic disturbances. Based upon the hypothesis that early, immediate reperfusion can

restore blood flow, the therapeutic window for successful intervention to restore the metabolic alterations has been postulated and proven to be within the first three hours from symptom onset. Other therapies include restoration of the cytokine, neurotransmitter, and  $\text{Ca}^{+2}$  concentrations within the infarct zone (see therapy for stroke below).

Since the therapeutic window for victims of stroke is narrow and the debilitating effects of an ischemic stroke can be both costly and severely impact health-related quality of life, there is demand for candidate therapeutic interventions that can halt, retard, prevent neural destruction. Furthermore, there is a demand to develop further candidate therapeutic interventions that can assist in the rehabilitation and ultimately improve the health-related quality of life indices.

#### Inflammation and Immune Disease, Disorders, or Dysfunctions

Exemplary diseases characterized by abnormal inflammatory or immunologic responses (also referred to herein as inflammatory or immune diseases or disorders) are described below. These diseases are suitable for application of the methods described in this invention for identification of variances in a gene or genes involved in therapeutic response, e.g. efficacy, tolerability or toxicity.

##### A. Arthritis

##### Description of Arthritis

Arthritis comprises a variety of diseases characterized by pain, swelling, and limited movement in joints and connective tissues. Arthritis is usually chronic and there are three prevalent forms of the disease: rheumatoid arthritis (RA), osteoarthritis (OA), and fibromyalgia. In RA, the synovial joint lining becomes inflamed as a result of hyperactive immune response. There are an estimated 2.1 million Americans with RA; two thirds are women. In OA, the cartilage that covers the ends of the bones within joints deteriorates, causing pain and loss of movement as bone begins to rub against bone. There are an estimated 20.7 million Americans with OA, the majority being over the age of 45. In fibromyalgia, widespread pain affects muscles, attachments of muscles to bone, and the connective tissues, i.e., the ligaments and tendons. There are an estimated 3.7 million individuals diagnosed with fibromyalgia syndrome. Other serious and common forms of arthritis or related disorders include the following: gout, systemic lupus erythematosus, scleroderma, ankylosing spondylitis, and juvenile arthritis.

Rheumatoid arthritis involves the disarthroidal joints and can affect a variety of other organs. The clinical hallmarks of RA include: morning stiffness; swelling of three or more joints; swelling of hand joints (proximal interphalangeal, metacarpophalangeal, or wrist); symmetric swelling; subcutaneous nodules; serum

rheumatoid factor; and erosions and or periarticular osteopenia, in hand or wrist joints, often observed on radiograph.

Osteoarthritis is a degenerative process in joint tissues that may occur in response to aging, genetic, and environmental factors. It is characterized by progressive degeneration of cartilage, bone remodeling, and overgrowth of bone. The clinical hallmarks of OA include: deep aching pain in the afflicted joints (hands, knees spine, and hips), morning stiffness of short duration, variable joint thickening and effusion. Pathologically OA is characterized by breakdown of cartilage. Destruction of joint cartilage involves direct physical injury, enzymatic degradation as a result of the injury to chondrocytes, and subchondral bone stiffening as a result of the bone remodeling.

#### Current Therapies for Arthritis

Agents used to treat RA fall into one of the following four categories: analgesics (NSAIDs, salicylates), disease modifying antirheumatic agents (gold compounds, cytotoxic), hormones (glucocorticoids), and skin and mucosal membrane preparations. Therapies for the treatment of OA focus on decreasing pain (analgesics) and physical therapies to increase joint mobility.

Analgesics: Typically, pain associated with arthritis can be controlled with NSAIDs including but not excluded to, salicylates, para-aminophenol derivatives, indole and indene derivatives, heteroaryl acetic acids, arylpropionic acids, anthranilic acids, enolic acids, or alkanones. Antiinflammatory agents such as cyclooxygenase inhibitors, lipoxxygenase inhibitors, and others can be used to block the inflammation physiological pathway which mediate pain and the progression of the disease. However, because these drugs are limited in their efficacy in advanced or more severe stages of arthritis, these agents are add-on therapies.

NSAIDs derive their principle mechanism of action by the inhibition of prostaglandin and leukotriene synthesis. These compounds inhibit key enzymes in the biosynthetic pathway, i.e. cyclooxygenase. There are drugs that selectively inhibit isoforms of cyclooxygenase 1 and 2 (COX-1, COX-2) which enhances patient tolerance due to the prevalence of COX-2 induction occurs in inflammation mediated by cytokines and others.

Further, pyrimidine synthesis inhibitors can be used as an antiinflammatory agent in arthritis, e.g. leflunomide.

Disease-Modifying Antirheumatic Drugs or agents: Agents involved in the modification of clinical disease manifestation, reduction in inflammation, or slow the progression of the disease are referred to as disease-modifying antirheumatic drugs (DMARDs) and include gold salts (aurothioglucose, aurothiomalate,

auranofin), hypotensives (angiotension converting enzyme inhibitors), anaprox, immunosuppressives (azathioprine, cyclosporine), agents to treat metallic poison (penicillamine), depen, naprosen, immuran, antimalarials (chloroquine, hydroxychloroquine), alkylating agents (cyclophosphamide), absorbable  
5 sulfonamides (sulfasalazine), irritants and counter-irritants (capsaicin), antimicrobial agents (tetracyclines), and antimetabolites (methotrexate).

Hormones and Growth Factors: Agents acting at hormone receptors or growth factor receptors include steroids (glucocorticoids), adrenocorticotrophic hormone (corticotropin), and tumor necrosis factor inhibitors (soluble TNF receptors  
10 (enbrel) and TNF monoclonal antibody (remicade). Since the autoimmunity component of the disease is driven primarily by activated T-cells, which give rise to cytokines IL-1 and TNF at the rheumatoid synovium. These agents are known to interfere with the actions of these cytokines.

Corticosteroids affect the inflammation within the joints by decreasing  
15 growth and development of mast cells, inducing apoptosis, suppressing lymphocyte generation of IL-5 and other cytokines, inhibiting some mediator release, inhibiting cytokine production, inhibiting the transcription of cytokines (for example IL-8, TNF- $\alpha$ , prototypic antiviral chemokine (regulated-on-activation normal T-expressed and secreted, RANTES), and GM-CSF), and inhibiting nitric oxide synthesis.

20 Skin and mucosal membrane preparations: irritants and counter-irritants can be used to treat arthritic joints and include, but not limited to, Capaicin

Chlorambucil, cyclosporine, cyclophosphamide are agents that are available for use in the treatment of refractory RA or with severe extraarticular complications such as vasculitits, corneal perforation or other severe systemic maladies associated  
25 with RA.

#### Low Efficacy Limitations of Therapies for Arthritis

The therapies discussed above are limited to the slowing or retarding the progression of arthritis. As degeneration of the joints progresses, and irreversible  
30 damage occurs, the options become limited. Thus, therapies for arthritis are aimed at reduction of manifestation of symptoms by controlling the clinical manifestations of inflammation.

The reduction of clinical symptoms of arthritis following DMARDs therapy is only evident after several weeks to months after therapy. The slow clinical  
35 relevance of these therapies limits the clinician to determine optimal therapy for individuals with arthritis, and provides a risk for selection of optimal therapy for any given stage of the disease.

Toxicity or Undesired Side Effects as Therapeutic Limitations of Arthritis

There are toxicities and undesired side effects associated with the above current therapies for arthritis that require monitoring. Drugs used to treat arthritis may cause death, disability, disease, and place an unborn child at risk. The undesired side effects or toxicities are listed for each drug category as described above.

Analgesics associated side effects include dyspepsia, gastric or small bowel bleeding, ulceration, renal insufficiency, confusion, rash, headache, hepatic toxicity. NSAIDs also reversibly inhibit platelet aggregation and prolong bleeding time.

Antirheumatic agents (DMARDs) associated side effects include antimalarials: retinal or macular damage; sulfonamides: hematologic toxicities (leukopenia, thrombocytopenia, hemolysis in patients with glucose 6-phosphate dehydrogenase (G6PD) deficiency); antimetabolites: hepatic compromise including hepatic fibrosis, ascites, esophageal varices, cirrhosis, pneumonitis, myelosuppression; immunosuppressives: myelosuppression, (cyclosporine: renal insufficiency anemia, hypertension); agents to treat metallic poison: rash, stomatitis, dysgeusia or metallic taste, myelosuppression (thrombocytopenia), proteinuria, nephrotic syndrome or renal failure, and induction of autoimmune syndromes (systemic lupus erythematosus, myasthenia gravis, polymyositis, Goodpasture's syndrome), gold preparations: hematologic, renal, pulmonary, and proteinuria; chlorambucil: myelosuppression, myeloproliferative disorders, malignancy, hemorrhagic cystitis.

Soluble TNF receptors agents have been shown to induce sepsis and predispose patients to serious infections. Further this product was associated with site of injection reactions, infections, and headache.

Glucocorticoid associated side effects include increased appetite, weight gain, fluid retention, acne, ecchymosis, development of cushoid facies, hypertension, hyperkalemia, diabetes, hyperglycemia, hyperosmolar state, hyperlipidemia, hepatic steatosis, atherosclerosis, myopathy, aseptic necrosis, osteoporosis, ulcers, pancreatitis, pseudotumor cerebri, psychosis, glaucoma, cataract formation, vascular necrosis, increased susceptibility to infection, impairment of the hypothalamus-pituitary axis, decreased thyroid hormone serum binding proteins, and impaired wound healing.

Since the majority of RA patients are women in their reproductive years, the level and extent the agents used to treat RA affects or has a potential to affect the mother during pregnancy, cross the placenta, affect the developing fetus, or be excreted in breast milk during lactation are important issues facing the skilled practitioner. Clinical medical therapeutic decisions must weigh the use of all of the

above current therapies for RA against known capacity of these agents to affect both the mother and the child.

Description of Mechanism of Action Hypotheses for Future Drug Development for Arthritis

Rheumatoid arthritis has been thought to be the result of host genetic factors, immunoregulatory abnormalities and autoimmunity, and triggering or persistent microbial infection.

Host genetic factors: the HLA-DR4 antigen (HLA, human leukocyte antigen) is significantly increased in RA patients. Recent studies have determined that a subtype of the HLA-DR4 share similar epitope among several MHC class II molecules and predispose to RA.

Autoimmune component: in over 80% of RA patients autoantibodies to the Fc portion of IgG (rheumatoid factors, RF) are present and can be used to determine diagnosis. The higher the titer of RFs the more severe joint disease and extrarticular manifestations.

Related to the autoimmune component of the disease, ICAM-1 inhibitors, or other agents to reduce adhesion have been developed.

Microbial Infections: of all the examined pathogens, only the Epstein-Barr virus (EBV) has remained unproven as a cause of RA. EBV has been shown to share a similar epitope as the HLA-DR4 epitopes, but EBV is ubiquitous and has yet to be a proven cause of RA.

A gene, genes, or gene pathway involved in the etiology of arthritis or associated disorders or potential sites for targeted drug therapy of arthritis are depicted in Table 9 with the specific gene list in Table 4. Current candidate therapeutic interventions in development for the treatment of arthritis are listed in Table 38.

**B. Chronic Obstructive Pulmonary Disease**

Description of Chronic Obstructive Pulmonary Disease

Chronic obstructive pulmonary disease (COPD) is an imperfect term that refers to four pulmonary disorders including simple chronic bronchitis, asthmatic bronchitis, chronic obstructive bronchitis, and emphysema. A common characteristic of the disease is airway obstruction. Airways obstruction denotes the slowing of forced expiration. A decrease in the forced expiratory volume in 1 second (FEV1) to forced vital capacity (FVC) indicates that airflow is impaired. Forced expiration is determined primarily by intrinsic resistance of the airways, compressibility of the airways, and lung elastic recoil. Reduced maximal expiratory



flow results from high airway resistance, reduced lung recoil, or excessive airways collapsibility. The overall cost of these illnesses to society is enormous due to the extent of the number of individuals afflicted with COPD, approximately 15 million Americans, and that COPD is currently the fourth-leading cause of mortality. The high morbidity and mortality rates associated with COPD are linked to the failure to identify at-risk patients and intervene. The lungs have large reserves of pulmonary function and the slow progressive nature of the disease can often delay the clinical diagnosis and therapeutic intervention.

Simple chronic bronchitis is a syndrome predominantly characterized by chronic productive cough and is usually the result of low-grade exposure to bronchial irritants. This syndrome is associated with enhanced mucous secretion, reduced ciliary activity, and impaired resistance to bronchial infection. Bronchitis patients range from those who experience sporadic cough producing mucous to those with a severe, disabling condition manifested by one or more of the following: increased resistance to airflow, hypoxia, hypercapnia, and irreversible narrowing of the small airways, i.e. bronchioles and bronchi (2 mm or less in diameter).

Repeated exposure to bronchiole irritants in individuals with hyperactive or sensitive airways can lead to bronchospasm, i.e. bronchial smooth muscle constriction, that is frequently accompanied by excess mucous production and edema of the bronchial walls. Episodic bronchospasm in individuals with chronic bronchitis is termed asthmatic bronchitis and is applied to those individuals with chronic airway constriction, chronic productive cough, and episodic bronchospasm.

Emphysema is characterized by abnormal, excessive, permanent enlargement of airway spaces distal to the terminal bronchioles, and is accompanied by destruction of their walls and may or may not be associated with fibrotic tissue. These changes result in a reduction of elastic recoil permitting excessive airway collapse upon expiration and leads to irreversible airway flow obstruction. Emphysema is strongly related to and correlated to inhalation of tobacco smoke, i.e. cigarette or cigar smoking.

In emphysema there is a loss of elastic recoil leading to pulmonary hyperinflation. The hyperinflation reaches a limit when the diaphragm is pushed flat and no longer functions effectively. The chest wall is expanded to the point that it pushes inward rather than exerting its normal outward force. These anatomical changes alter inspiration to the point that exertion is nearly impossible.

A deficiency in alpha 1- antitrypsin can predispose individuals to signs and symptoms of COPD. In these individuals there is a marked alveolar wall destruction with a non-uniform pattern of air space enlargement. In these patients there may be excessive formation of thick mucous and is often accompanied by persistent cough.

Complications of COPD include hypoxemia, cor pulmonale, hypercapnia, and dyspnea. Sustained chronic hypoxemia is a condition that leads to pulmonary vasoconstriction that with time becomes irreversible and leads to cor pulmonale.

#### Current therapies for COPD

The current therapies is use for the treatment of subjects with COPD are aimed at reducing the airway obstruction that is reversible, controlling the persistent cough and sputum production, reducing or eliminate airway infections, increasing exercise tolerance to the maximum allowable at the individual's level of physiological deficit, controlling the remedial disease complications, i.e. cardiovascular dysfunction and arterial hypoxemia, and relief of the anxiety and depression or other psychiatric symptoms that accompany patients attempts to cope with the debilitating clinical manifestations. Lastly, all treatment regimens include education and supportive therapy to encourage subjects with COPD to cease behaviors that may exacerbate symptoms such as inhalation of pulmonary irritants, i.e. smoking and others, and substance abuse, i.e. narcotics and sedatives.

#### Bronchodilators

Bronchodilators can be inhaled, or by oral, subcutaneous, or intravenous routes.

Beta-adrenergic agonists or other sympathomimetic agents are used to produce rapid acute bronchodilation.

Anticholinergics agents are used to produce sustained bronchodilation. Nebulized atropine has been supplanted with the advent of a quaternary ammonium salt, ipratropium bromide, which undergoes minimal systemic absorption and thus has limited anticholinergic toxicity. Ipratropium has been shown to be effective in patients that have not responded to  $\beta$ -adrenergic agonists and can reduce sputum volume without altering viscosity.

Anticholinergics and beta-adrenergic agonist combinations have been used with some success. Such combinations reduce the need to administer high doses, due to additive effects, and therefore reduce the likelihood for adverse effects or toxic side effects.

Theophylline is a methylxanthine bronchodilator. Theophylline improves airway flow, decreases dyspnea, reduces pulmonary arterial pressure, increases arterial oxygen tension, improves diaphragmatic strength and endurance, increases right ventricular function (pulmonary vasodilator and cardiac inotropic effects), and may produce antiinflammatory effects.

#### Expectorants

Expectorants can be used to increase the secretion clearance in patients with COPD. Although this therapy has not been demonstrated to render clinical benefit, it is as add on therapy that enables the patient to experience an enhanced productive cough.

5        Anti-Inflammatory agents

Prolonged use of corticosteroids have been used to retard the rate of decline in FEV1 in COPD subjects. However, it has been determined that systemic corticosteroids are beneficial for acute exacerbations of COPD but are not used for long-term treatment and have not been proven to retard the progression of the  
10       disease. Corticosteroids affect the decline of FEV1 in the airways by decreasing growth and development of mast cells, inducing apoptosis, suppressing lymphocyte generation of IL-5 and other cytokines, inhibiting some mediator release, inhibiting cytokine production, inhibiting the transcription of cytokines (for example IL-8, TNF- $\alpha$ , prototypic antiviral chemokine (regulated-on-activation normal T-expressed and secreted, RANTES), and GM-CSF), and inhibiting nitric oxide synthesis.  
15

Antiproteases and antioxidants

Alpha1-protease inhibitor deficiency as a cause of early development of emphysema has increased the awareness of the role of protease-antiprotease and oxidant-antioxidant imbalances in COPD. Intravenous delivery of alpha 1-protease  
20       inhibitor can provide the appropriate levels in those individuals with a genetic deficiency and those whose deficiency is acquired.

Mucolytics and secretion clearance agents can be used to assist in the removal of secretions during productive cough. These agents can thin secretions in patients with chronic bronchitis.

25       Supplemental oxygen therapy is used to treat the deleterious effects of sustained chronic hypoxemia and hypercapnia. Correction of this condition is one of the treatments shown to have a positive effect on the survival rate in patients with COPD.

30       Treatment of cases of cor pulmonale includes the use of diuretics and positive inotropic agents such as digitalis. Careful monitoring is required in these patients due to a development of marked right ventricular hypertrophy.

Dyspnea may be severely disabling despite aggressive therapy. Judicious use of opiates to control dyspnea and increase exercise tolerance have been proven to be beneficial. Unfortunately, opiates can have a respiratory depressant effect and  
35       care must be taken to deliver the appropriate therapeutic dose.

Many patients with COPD find themselves anxious or depressed or both. Appropriate use of psychoactive agents can be used to control the signs and symptoms of anxiety and depression.

Surgical procedures can be performed to attempt to restore pulmonary capacity and function. Lung volume reduction surgery is useful to remove a portion of emphysematous lung tissue so that the diaphragm can return to its normal dome shape and the chest wall can reassume its normal configuration, mechanics, and physiology. Bullectomy is a procedure in which large bullae and surrounding lung tissue are removed. This allows for the remaining tissue to expand and once again function normally. Another procedure is lung transplantation. This expensive and aggressive approach is usually reserved for younger patients, particularly those who are alpha 1-antitrypsin deficient.

#### Limitations of Current Therapies for COPD

The most common limitations for the use of bronchodilators is the mistaken use of inhalants and inadequate patient education.

Beta adrenergic therapy is limited by three factors: 1) the density of  $\beta_2$  receptors in the airways decreases with age, 2) despite the selectivity of the  $\beta_2$  receptor agonists, there is cross reactivity to  $\beta_1$  receptors and may affect the myocardium and other peripheral tissues, and 3) there is  $\beta$ -adrenergic receptor desensitization. Most of the recommended doses of beta adrenergic agonists provide less than maximal bronchodilation. Beta-adrenergic agonists can cause tremor, reflex tachycardia, tachyphylaxis, cardiomyopathy, and other cardiac toxic effects. Tachycardia is particularly problematic in the elderly or for those individuals who are at cardiac risk. Further,  $\beta$ -adrenergic agonists have been shown to cause hyperkalemia. The majority of patients with COPD are current or former smokers, all of whom are may have coexisting coronary artery disease, thus in the compendium of therapies it is desirable to have alternatives to  $\beta$ -adrenergic agonists.

Anticholinergics as bronchodilators have been associated with systemic side effects. In particular, systemic anticholinergic side effects include bradycardia (if pronounced, includes compensatory tachycardia), dry mouth, inhibition of sweating, dilatation of the pupils, and visual blurring. Ipratropium has a slow onset of action and a longer duration of action than  $\beta$ -adrenergic agonists which can be deleterious for acute bronchodilation because patients continue to administer the drug without effect and overdose.

Theophylline continues to be a controversial treatment due to misconceptions of its role as a bronchodilator, drug delivery problems, and conflicting results of comparative studies during acute exacerbations. Further, theophylline has a limited therapeutic window, i.e. the dose required to achieve bronchodilation is close to the dose associated with undesirable or adverse side effects including convulsions,

cardiac arrhythmias, tachycardia, vasodilation, and diuresis. Further complicating therapy with theophylline is the intra-patient variability in efficacious response.

Long-term use of corticosteroids can be useful for patients in which continued symptoms or severe airflow limitations exist despite therapy with other agents. Only 20-30% of these patients experience therapeutic benefit for long-term use and indiscriminate use often leads to adverse effects without benefits. Unfortunately there have not been identified predictors of responders or nonresponders to long term steroid use in patients with COPD. Therefore, only those patients that attempt long-term steroid use and have documented clinical improvement should continue steroid therapy. Unfortunately, those patients in which long-term steroid use results in no benefit are subjected to potential adverse effects or toxicities. Glucocorticoid associated side effects include increased appetite, weight gain, fluid retention, acne, ecchymosis, development of cushoid facies, hypertension, hyperkalemia, diabetes, hyperglycemia, hyperosmolar state, hyperlipidemia, hepatic steatosis, atherosclerosis, myopathy, aseptic necrosis, osteoporosis, ulcers, pancreatitis, pseudotumor cerebri, psychosis, glaucoma, cataract formation, vascular necrosis, increased susceptibility to infection, impairment of the hypothalamus-pituitary axis, decreased thyroid hormone serum binding proteins, and impaired wound healing.

Mucolytic and secretion clearance agents have been shown to improve thinning secretions however, there is little evidence to suggest that these agents render clinical improvement. Further cough suppressants may impair secretion clearance and possibly increase the risk of pulmonary infection.

*Description of Mechanism of Action Hypotheses for Future Drug Development of Candidate Therapeutic Interventions of COPD*

Since the predominant category of patients with COPD were or are current smokers smoking cessation programs and agents used to help patients quit smoking will be a valuable addition to therapeutic regimens. Nicotine replacement therapies such as nicotine patches (transdermal), gum, and transnasal formulations as well as bupropion (an antidepressant or other in this category) should be considered.

Other therapies to be considered are novel bronchodilators for inhalation therapy without the use of chlorofluorohydrocarbons (CFCs), next generation anticholinergic therapies, alpha 1 antiproteinase augmentation therapies, and refinement of surgical procedures.

A gene, genes, or gene pathway involved in the etiology of COPD or associated disorders or potential sites for targeted drug therapy of COPD are depicted in Table 9 with the specific gene list in Table 4. Current candidate

therapeutic interventions in development for the treatment of COPD are listed in Table 39.

### C. Autoimmune Disease

#### Description of Autoimmune disease

An immune response to “self” antigens, or autoimmunity, can vary from minimal to severe depending on the extent of the loss of self tolerance and to the localization of the antigens. There is then a distinction between autoimmune response which may or may not be pathologic and autoimmune disease which does lead to pathologic conditions. In autoimmune disease there is a combination of the following types of evidence, 1) identification of the target antigens, 2) identification and isolation of self-reactive autoantibodies or self-reactive lymphocytes, 3) identification of clinical evidence, i.e. familial hereditary data, lymphocyte infiltration, MHC association and clinical symptomatic improvement with immunosuppressive agents. Initiation of autoimmune disease is thought to require one or more of the following: genetic predisposition to loss of tolerance, environmental factors that stimulate aberrant immune response, or loss or dysfunction of cellular or organ physiological processes leading to pathological immune response. Since many autoreactive clones of T and B cells exist and are normally regulated by homeostatic mechanisms, loss or breakdown of this system of checks and balances can lead to activation or enhancement of these autoreactive clones and ultimately lead to autoimmune disease.

There are a few autoimmune disease indications whereby inflammation and immune response gene pathways should be considered in the stratification or therapeutic choice of patient groups based upon genotype. There are multiple examples of autoimmune diseases or diseases that have an autoimmune component including: amyotrophic lateral sclerosis, anti-phospholipid syndrome, aplastic anemia, autoimmune hemolytic anemia, diabetes mellitus type 1, Guillan-Barre syndrome, idiopathic thrombocytopenic purpura, Grave’s disease, myasthenia gravis, polymyositis, rheumatoid arthritis, Hashimoto’s thyroiditis, uveitis, Wegener granulomatosis, periarteritis nodosa, ocular pemphigoid, pemphigus vulgaris, psoriasis, Goodpasture’s syndrome, Churg-Strauss vasculitis, poly-dermatomyositis, Cogan syndrome- autoimmune inner ear disease, hemolytic uremic syndrome, idiopathic glomerulonephritis, inflammatory bowel disease, Crohn’s disease, microscopic polyarteritis, and multifocal motorneuron neuropathy. Here we discuss four specific diseases that represent larger patient populations and are representative of diseases in which therapy can be aimed at suppressing the hyperactivity of the

immune system. These include multiple sclerosis, systemic lupus erythmatosus, scleroderma, diabetes mellitus type I, sarcoidosis, and nephritis.

#### Multiple Sclerosis

Multiple sclerosis (MS) is a disorder of multifocal sites of myelin sheath  
5 destruction, perivascular-lymphocytic cuffing and variable degree of  
oligodendroglial loss. In profound cases, there is gliosis, axonal transection, and  
neuronal and axonal loss. There are an estimated 300,000 Americans diagnosed  
with MS. The estimated cost of MS is \$5 billion dollars.

Clinically, MS begins with a relapsing illness with episodes of neurological  
10 dysfunction lasting several weeks, followed by substantial or complete  
improvement. This is identified as the relapsing-remitting stage of the disease found  
to be predominantly in females (1.6:1). There are some patients that remain in this  
stage of the disease for decades; others may rapidly progress to the next stage. As  
time progresses, and repeated relapses occur, recovery becomes less and less  
15 complete or as substantial. In these cases, a gradual relapse independent clinical  
progression develops and is termed secondary progressive MS. Further, the  
nonrelapsing-nonremitting form is characterized by a gradual progression and steady  
worsening of neurological function without any recovery or improvement. A steady  
but gradual neurological decline and predominately identified in males characterizes  
20 the primary progressive form of MS. Clarity in understanding the significance of  
these varying disease patterns and diagnosis is dependent on quality neurological  
examination overtime.

#### Systemic Lupus Erythmatosus

Systemic lupus erythmatosus (SLE) is a disease characterized by  
25 inflammation in many different organ systems associated with the production of  
antibodies to reactive to nuclear, cytoplasmic, and cell membrane antigens. Clinical  
manifestations of the disease include reddish rash on the cheeks, fatigue, anemia,  
rashes, sun sensitivity, alopecia, arthritis, pericarditis, pleurisy, vasculitis, nephritis,  
and central nervous system disease. The immune hypereactivity appears to derive  
30 from immune hypereactivity and loss of self-tolerance. In these patients antibodies  
are produced against several nuclear components, notably antinuclear antibodies to  
native double stranded DNA, single stranded DNA, or nucleohistones.

#### Scleroderma

Scleroderma is a chronic disease marked by increases of fibrotic tissue  
35 involving the circulatory system, connective tissue (in particular the skin), visceral  
organs, and the immune system. There are approximately 500-700,000 Americans  
diagnosed with scleroderma. There are two types of scleroderma, localized and  
systemic. In localized scleroderma (linear and morphea) the disorder of the

connective tissue is limited to the skin, the tissues just beneath the skin, and muscle. Internal organs are not affected. In systemic scleroderma (sclerosis) vascular, digestive, pulmonary, renal, muscle and joints may be affected. Raynaud's syndrome (frequent spasms of small arteries induced by temperature changes and emotion resulting in deprivation of blood supply to peripheral tissues), CREST syndrome (calcium deposits, Reynaud's syndrome, loss of muscular control of the esophagus, sclerodactylia, and telangiectasia), and Sjogren's syndrome (inflammation of the conductive, cornea, tear, and salivary glands with progressive destruction by lymphocytes and plasma cells) are both subcategories of scleroderma.

The clinical manifestations of scleroderma include the following symptoms: fatigue, swelling and numbness of the hands and feet, shiny skin and disappearance of skin folds, ulcers on the fingers, calcium deposits on the fingers, joint inflammation, joints tightening into bend position, muscle weakness, itchy skin, difficulty in swallowing, shortness of breath, fatty diarrhea or constipation, and loss of body hair. Although ultimately renal impairment and failure is a common endpoint, therapy affecting the hypertensive phase or renal involvement has changed the mortality rate.

#### Diabetes Mellitus type I

This form of diabetes involves the chronic inflammatory destruction of the insulin-producing islet cells of the pancreas. Although this form of diabetes is treated similarly to the type II form (which is not linked to autoimmunity), i.e. insulin replacement therapy, early identification of type I versus type II individuals may be useful to thwart the autoimmune destruction of the  $\beta$ -cells. There are an estimated 500,000 to 1 million Americans that have type I diabetes, it is the seventh leading cause of death, and the following is a list of the progressive complications that are associated with the unregulated carbohydrate balance in tissues: retinopathy leading to blindness, nephropathy (diabetic nephropathy is the leading cause of end-stage renal disease), coronary and cardiovascular disease, neuropathy (severe forms can lead to amputation), impotence (diabetic neuropathy and cardiovascular disease can lead to impotence), and stroke.

#### Sarcoidosis

Sarcoidosis is a granulomatous disorder characterized by enhanced cellular immune response at one or more involved sites. The prevalence of sarcoidosis is 5 in 100,000, so approximately 13,000 patients have been diagnosed. Between 80-90% of patients with sarcoidosis have pulmonary involvement, however, any organ can be affected. Pulmonary involvement includes dyspnea with or without exertion, persistent dry cough, and atypical chest pain. Cor pulmonale can develop as a complication of pulmonary dysfunction and further progress to right atria dilatation



and right ventricular hypertrophy. Ocular involvement includes disturbance in visual acuity, and in chronic cases may lead to glaucoma, cataract formation and retinal neovascularization. In 80% of the cases, sarcoidosis is self-limiting and results in minimal symptomology, discomfort, or debilitation. However in the remaining 20%, sarcoidosis patients face potentially serious debilitation, disfigurement, and can be life threatening. Misdiagnosis is frequent and can limit appropriate therapeutic intervention.

#### Nephritis

Inflammation of the kidneys results in impaired renal function. Nephritis can be either interstitial or glomerular. In either case, mononuclear cells infiltrate in the interstitium of the renal cortex. Eosinophils, and in some cases, polymorphonuclear leukocytes are found in a similar compartment. The infiltrate may be diffuse or patchy and may be accompanied by fibrotic tissue. Membranous nephropathy may develop and lead to impairment of glomerular filtration rate. There is evidence to suggest both cytotoxic T cells and T-cell mediate delayed hypersensitivity are involved. Nephritis is a component of the clinical manifestation of systemic lupus erythematosis, scleroderma, and other autoimmune diseases and disorders.

#### Current therapy for Autoimmune Diseases and Disorders

Agents used to treat autoimmune disease fall into one of the following four categories: analgesics (NSAIDs, salicylates), immunosuppressive agents, hormones (glucocorticoids), and skin and mucosal membrane preparations

Analgesics: Typically, pain associated with autoimmune disease can be controlled with NSAIDs including but not excluded to, salicylates, para-aminophenol derivatives, indole and indene derivatives, heteroaryl acetic acids, arylpropionic acids, anthranilic acids, enolic acids, or alkanones. Antiinflammatory agents such as cyclooxygenase inhibitors, lipoxigenase inhibitors, and others can be used to block the inflammation physiological pathway which mediate pain. However, because these drugs are limited in their efficacy in advanced or more severe stages of autoimmune disease, these agents are add-on therapies.

NSAIDs derive their principle mechanism of action by the inhibition of prostaglandin and leukotriene synthesis. These compounds inhibit key enzymes in the biosynthetic pathway, i.e. cyclooxygenase. There are drugs that selectively inhibit isoforms of cyclooxygenase 1 and 2 (COX-1, COX-2) which enhances patient tolerance due to the prevalence of COX-2 induction occurs in inflammation mediated by cytokines and others.

Immunosuppressive drugs or agents: Agents involved in the modification of the immune system for the treatment of autoimmune disease are immunosuppressive

agents. Immunosuppressives include azathioprine, cyclosporine, penicillamine, antimalarials (chloroquine, hydroxychloroquine), alkylating agents (cyclophosphamide), and antimetabolites (methotrexate).

Hormones and Growth Factors: Agents acting at hormone receptors or growth factor receptors include steroids (glucocorticoids), adrenocorticotrophic hormone (corticotropin), and tumor necrosis factor inhibitors (soluble TNF receptors (enbrel) and TNF monoclonal antibody (remicade). Since the autoimmunity component of the disease is driven primarily by activated T-cells, which give rise to cytokines IL-1 and TNF at the affected areas. These agents are known to interfere with the actions of these cytokines.

Corticosteroids affect the immune response by decreasing growth and development of mast cells, inducing apoptosis, suppressing lymphocyte generation of IL-5 and other cytokines, inhibiting some mediator release, inhibiting cytokine production, inhibiting the transcription of cytokines (for example IL-8, TNF- $\alpha$ , prototypic antiviral chemokine (regulated-on-activation normal T-expressed and secreted, RANTES), and GM-CSF), and inhibiting nitric oxide synthesis.

Plasma Exchange: A useful technique for the removal of autoantibodies is a process called plasmaphoresis or plasma exchange. In this process, antibodies are removed that mediate humoral immune response to the autoantigen.

Antioxidants: Many of the therapies in use for these autoimmune diseases are aimed at reducing the level and extent of tissue damage mediated by T-cell immune response. For example, dimethyl sulfoxide, dimethyl sulfone, para-aminobenzoic acid, and vitamin E are included in this category.

#### Limitations Current Therapies for Autoimmune Disease based upon Low efficacy

The therapies discussed above are limited to the slowing or retarding the progression of autoimmune disease. As immune response tissue damage occurs, degeneration of the function progresses, irreversible damage occurs, and therapeutic options become limited. Thus, therapies for autoimmune disease are aimed at reduction of manifestation of symptoms by controlling the clinical manifestations of inflammation and the hypersensitive immune response.

The reduction of clinical symptoms of autoimmune disease following immunosuppressive therapy by one of the agents listed above is only evident after several weeks to months after therapy. The slow clinical relevance of these therapies limits the clinician to determine optimal therapy for individuals with autoimmune disease, and provides a risk for selection of optimal therapy for any given stage of the disease. Furthermore, there may be delays in identifying those

patients that have an autoimmune hyperreactivity, and this can delay therapeutic intervention.

5     Limitations Current Therapies for Autoimmune Disease based upon Toxicity or Undesired side effects

There are toxicities and undesired side effects associated with the above current therapies for autoimmune disease that require monitoring. Drugs used to treat autoimmune disease may cause death, disability, disease, and place an unborn child at risk. The undesired side effects or toxicities are listed for each drug category as described above.

Analgesics associated side effects include dyspepsia, gastric or small bowel bleeding, ulceration, renal insufficiency, confusion, rash, headache, hepatic toxicity. NSAIDs also reversibly inhibit platelet aggregation and prolong bleeding time.

Immunosuppressive therapies have associated side effects including antimalarials: retinal or macular damage; sulfonamides: hematologic toxicities (leukopenia, thrombocytopenia, hemolysis in patients with glucose 6-phosphate dehydrogenase (G6PD) deficiency); antimetabolites: hepatic compromise including hepatic fibrosis, ascites, esophageal varices, cirrhosis, pneumonitis, myelosuppression; immunosuppressives: myelosuppression, (cyclosporine: renal insufficiency anemia, hypertension); penicillamine: rash, stomatitis, dysgeusia or metallic taste, myelosuppression (thrombocytopenia), proteinuria, nephrotic syndrome or renal failure, and induction of autoimmune syndromes (systemic lupus erythmatosus, myesthenia gravis, polymyocytis, Goodpasture's syndrome).

Glucocorticoid associated side effects include increased appetite, weight gain, fluid retention, acne, ecchymosis, development of cushoid facies, hypertension, hyperkalemia, diabetes, hyperglycemia, hyperosmolar state, hyperlipidemia, hepatic steatosis, atherosclerosis, myopathy, aseptic necrosis, osteoporosis, ulcers, pancreatitis, psuedotumor cerebri, psychosis, glaucoma, cataract formation, vascular necrosis, increased suseptibility to infection, impairment of the hypothalamus-pituitary axis, decreased thyroid hormone serum binding protiens, and impaired wound healing.

Since the majority of autoimmune disease patients are women in their reproductive years, the level and extent the agents used to treat autoimmune disease affects or has a potential to affect the mother during pregnancy, cross the placenta, affect the developing fetus, or be excreted in breast milk during lactation are important issues facing the skilled practitioner. Clinical medical therapeutic decisions must weigh the use of all of the above current therapies for autoimmune disease against known capacity of these agents to affect both the mother and the child.

Description of Mechanism of Action Hypotheses for Future Drug Development for the Treatment of Autoimmune Disease

Autoimmune disease has been thought to be the result of host genetic factors, immunoregulatory abnormalities and autoimmunity, and triggering or persistent microbial infection.

A gene, genes, or gene pathway involved in the etiology of autoimmune diseases or disorders or associated disorders or potential sites for targeted drug therapy of autoimmunity are depicted in Table 9 with the specific gene list in Table 4. Current candidate therapeutic interventions in development are listed for the treatment of autoimmune disease or disorder, Tables 40 and 42, and for systemic lupus erythematosus, Table 41.

D. Immunosuppression- Transplantation

Description of Transplantation

There are many different conditions in which medical or surgical therapy is unable to halt, retard, or treat the underlying disease, disorder, or dysfunction. Although many refractory diseases, disorders, or dysfunctions do not lead to severe cases, there are some in which the progression leads to conditions in which the remaining therapeutic alternative is replacement of the diseased tissue with normal donated tissue by transplantation. These end stage conditions include both primary disease or complications from a disease. For example whole organ transplantation is an end-stage therapeutic alternative in the following indications, end-stage cardiomyopathy, end-stage renal disease, pulmonary disease, cirrhosis of the liver, as well as other end-stage diseases affecting whole organ function.

Besides whole, or partial organ transplantation there are programs aimed at replacing cells in specific tissues to enable or restore physiologic function. For example cellular transplantation includes, but not excluded to, grafting bone marrow cells in patients with hematopoietic or lymphocytic cancers, dopaminergic producing cells in brains of patients with Parkinson's disease, striated muscle cells in patient's with Duchenne's muscular dystrophy, myocytes or cardiomyocytes in patient's with ischemic heart disease or cardiomyopathy, and replacement of neurons or astrocytes or glial cells in neurodegenerative disease including but not excluded to Alzheimer's disease, amyotrophic lateral sclerosis, multiple sclerosis, Huntington's disease, refractory pain, epilepsy, and stroke.

In this way, transplantation includes autografts, isografts, allografts or xenografts and can involve whole organ or cellular grafts. With the exception of autologous transplantation, all other transplantation procedures include pre- and

post-surgical immunosuppression to blunt graft rejection or graft versus host disease. Successful immunosuppression in this setting includes an appropriate balance between the need to prevent the process of graft rejection and the risk of suppressing the recipient's immune system to the extent that they become vulnerable to infection or other complications.

Transplantation is immunologically mediated. Both T cells and circulating antibodies are induced against allografts or xenografts. While the antibodies are responsible for rejection of erythrocytes, T-cells are mainly responsible for the rejection of most other type of tissue. The antigens found on grafted tissue which initiate the rapid rejection of an allograft are found on most cell membranes and are encoded by genes in the major histocompatibility complex (MHC) which are called the HLA. The structures encoded in these genes, MHC class I and class II molecules, are involved in the determining the discrimination between self and non-self. The degree of the histocompatibility between donor and recipient can be determined serologically, by genotyping, or by a mixed lymphocyte reaction. Survival of HLA nonmatched allografts is prolonged by anti-inflammatory agents, cytotoxic agents, antimetabolites, and other modalities aimed at immunosuppressing the recipient. These approaches have proven clinical success in terms of graft survival and clinical symptomology.

Rejection can occur at any time, and is either hyperacute, acute or delayed. The rate, extent, and underlying mechanism of transplantation rejection varies dramatically from individual to individual. Physiological factors include patency of blood circulation, lymphatic drainage, expression of antigens on the graft, and others that can influence the rejection rate.

In hyperacute rejection, preexisting host antibodies to antigens found on the grafted tissue mount an immune response. These antibodies activate complement, followed by platelet activation and deposition causing swelling and interstitial hemorrhage in a whole organ graft, or specific cell targeting in a cellular transplant. Cell mediated immunity is not activated in the hyperacute response.

In acute rejection, infiltration of lymphocytes and macrophages recognize the foreign antigen on the graft cells, and initiate a cascade of intragraft events that ultimately leads to host cellular and humoral mediated destruction of the grafted tissue and if unchecked will result in irreversible loss of the graft. This acute process occurs rapidly and does not in the first stages affect the vital structures of a whole organ graft, which allows for identification of the process and implementation of therapy. In many cases, an acute rejection episode can be reversed, and approximately 30-50% of whole organ graft recipients undergo one or more of these episodes in the early transplant period.

Delayed or chronic rejection occurs in a slower process than acute rejection and ultimately leads to a gradual loss of function in the grafted tissues. In chronic or delayed rejection, both cell mediated immunity and humoral immunity is activated. Chronic rejection is characterized by arteriosclerosis, in which the smooth muscle cells lining the arteries in the graft organ proliferate to create lesions and lead to fibrosis, with a result of constricting blood flow. As a result of the chronic immune rejection, there is slow and progressive destruction of the grafted organ or cells. If damage to the tissue is extensive, very little can be done to save the graft.

#### Current Immunosuppressive Therapies

The goal of clinical immunosuppression in the transplantation setting is to control allograft rejection. Clinical immunosuppression involves the non-specific suppression of both cell-mediated and humoral immune reactivity to the grafted tissue. Although a number of methods have been proposed, successful prolongation of graft survival has been attained through the use of a combination of therapies that suppress both the lymphocytic interaction and proliferation and therapies that deplete the pool of available lymphocytes.

##### Antiproliferative agents

These agents are useful to blunt the proliferative phase of lymphocyte activation of the immune response.

##### Purine analogs

Azathioprine acts to inhibit the proliferation of T cells. Azathioprine is cleaved to 6-mercaptopurine and it is this active compound that serves to suppress the T-cell mediated antigenic determination and engraftment. Azathioprine is a relatively non-selective immunosuppressive agent. Other agents in the same class as azathioprine, i.e. antimetabolites, include but are not excluded to, mercaptopurine, chlorambucil, and cyclophosphamide.

##### Pyrimidine analogs

The agents (cytosine arabinoside) inhibits DNA synthesis and therefore have their greatest effect on the immune response during the proliferative phase of lymphocyte activation. These agents inhibit primary antibody response and have minimal effects on the cell-mediated immunity.

##### Folic acid analogs

These agents (methotrexate, aminopterin) inhibit dihydrofolate reductase preventing the conversion of folic acid to tetrahydrofolic acid. This conversion is necessary for the production of DNA and RNA.

##### Alkylating Agents

These agents (nitrogen mustard, phenylalanine mustard, busulfan, cyclophosphamide) alter the structure of the DNA and RNA. These agents have reactive ring structures which combine with electron rich groups such as tertiary nitrogen in purines or pyrimidines, or -NH<sub>2</sub>, -COOH, -SH, -PO<sub>3</sub>H<sub>2</sub> groups. These reactions alter the composition of the DNA, and if not repaired, chromosomal replication will be altered in activated proliferating cells. The use of alkylating agents in the setting of transplantation is time dependent and is effective just before or during the activation of the immune system by antigen. Cyclophosphamide has been shown to have a greater effect on B-cells rather than T-cells, thereby inhibiting the humoral response to a greater degree.

#### Antibiotics

These agents (actinomycin D, mitomycin C, puramycin, chloramphenicol) inhibit either nucleic acid or protein synthesis.

Cyclosporin acts by inhibiting the production of IL-2, which results in an inhibition of the proliferation of T and B lymphocytes. Cyclosporin is widely prescribed for transplantation patients due to the clinical advantage of potent immunosuppression with limited myelosuppression.

FK-506 (Tacrolimus) is an agent that acts by inhibiting the production of IL-2 which prevents the proliferation of T and B lymphocytes.

Mycophenolate mofetil is rapidly converted to mycophenolic acid which selectively inhibits T and B cell proliferation. Mycophenolate mofetil has an advantage over azathioprine because it does not damage chromosomes.

#### Lymphocyte Depletion agents

Antilymphocytic globulin (ALG) is an agent that binds to circulating T-lymphocytes and the cells coated with the ALG are lysed and cleared by the reticuloendothelial system. ALG is more commonly used for renal transplantation, showing little to no benefit for liver or bone marrow transplantation..

#### Radiation

Total lymphoid irradiation or total body irradiation is based upon the immunosuppression observed after this procedure was used in patients with Hodgkin's lymphoma. The radiation causes breakdown in the nucleic acid structure, and the effect is time dependent since there are systems within all cells for the repair of DNA. Since the radiation affects those cells in M or G<sub>2</sub> phase, those cells in G<sub>1</sub> or S phase are resistant.

#### Monoclonal antibodies

A murine monoclonal antibody is available to deplete the circulating CD3 lymphocytes. This antibody reacts with the T3 recognition site of the T-lymphocytes and blocks the recognition of the Class I and II antigens. This leads to

prevention of the activation of the effector lymphocytes. This antibody has been useful in the treatment of rejection of renal, pancreatic, hepatic, cardiac, and pulmonary whole organ transplantations.

Steroids- such as the glucocorticoids are widely used in transplantation in combination with other drugs. As well as providing antiinflammatory therapy, corticosteroids suppress immune function by inhibiting the activation of T cells. Corticosteroids affect the inflammation within the airways by decreasing growth and development of mast cells, inducing apoptosis, suppressing lymphocyte generation of IL-5 and other cytokines, inhibiting some mediator release, inhibiting cytokine production, inhibiting the transcription of cytokines (for example IL-8, TNF- $\alpha$ , prototypic antiviral chemokine (regulated-on-activation normal T-expressed and secreted, RANTES), and GM-CSF), and inhibiting nitric oxide synthesis. Steroids are highly effective in the early induction and maintenance regimens and are first line therapy in acute allograft rejection.

Blood transfusions can be used to cause allosensitization if the recipient is exposed to donor antigens in the presence of azathioprine. In this way, induction of a specific degree of hyporeactivity against graft antigens can result by a potential suppressor cell phenomena.

#### Limitations of Immunosuppressive Therapies due to Lack of Efficacy

As suggested, the efficacy of immunosuppression is a balance between prevention of graft rejection or graft versus host disease and subjecting a patient unnecessarily to blunted immune defenses to ward off infections. All too often, this balance is not achieved and on one end the patient succumbs to infections or on the other the graft is rejected. It has been estimated that 30% of the transplantation patients are in this category.

#### Limitations of Immunosuppressive Therapies due to Toxicities or Undesired Side Effects

##### Antiproliferative Agents

Azathioprine is associated with suppression of bone marrow production, and blood disorders including anemia, thrombocytopenia, and leukopenia.

Hepatotoxicity occurs in a dose-independent manner, and is irreversible.

Azathioprine is associated with chromosome damage and therefore is mutagenic.

Methotrexate and aminopterin are associated with bone marrow suppression, mucosal breakdown, gastrointestinal bleeding, megaloblastic hematopoiesis.



Alkylating Agents are associated with stomatitis, nausea, vomiting, diarrhea, skin rash, anemia, and alopecia. Specifically, cyclophosphamide has been associated with fluid retention, hemorrhagic cystitis, and cardiac toxicity.

5 Cyclosporin is associated with gingival hyperplasia, hirsutism, tremor, hypertension, hyperkalemia, hepatotoxicity, hyperglycemia, hypomagnesiumemia, hypercholesterolemia, hypertriglyceridemia, and hyperuricemia, nausea and gastrointestinal irregularities, and renal dysfunction. Nephrotoxicity associated with cyclosporin manifests as tubular necrosis, interstitial fibrosis, and tubular atrophy.

10 FK506 is associated with neurotoxicity, nephrotoxicity, and disturbances of glucose metabolism. The major neurotoxic symptoms are reversible and dose dependent and include headache, tremors, parasthesias, insomnia, increased sensitivity to light, mood changes, aphasia, and seizures. There has been a suggested association of FK-506 with cardiomyopathy and it is contraindicated in pregnancy.

15 Lymphocyte Depletion Agents

ALGs are associated with anemia, thrombocytopenia, and allergic reactions including urticaria, anaphylactoid reactions, serum sickness, joint pain, fever, and malaise.

20 Radiation is associated with higher incidence of infections and chromosomal breakage and mutations.

Monoclonal antibody therapy has been associated with the production of human anti-mouse antibodies (HAMA) in 80% of the treated patients and the sensitization rate is 15-40% thus limiting retreatment rates. Side effects are fever, chills, nausea, vomiting, headache, dyspnea, wheezing, pulmonary edema, 25 tachycardia, hypotension, aseptic meningitis, seizures, and coma. These symptoms are related to the inordinate release of cytokines TNF, IL-1, and interferon-gamma. Although these symptoms can be reduced by pretreatment with steroids, acetaminophen, or diphenhydramine the HAMA response precludes repeated use.

30 Steroids- Glucocorticoid associated side effects include increased appetite, weight gain, fluid retention, acne, ecchymosis, development of cushoid facies, hypertension, hyperkalemia, diabetes, hyperglycemia, hyperosmolar state, hyperlipidemia, hepatic steatosis, atherosclerosis, myopathy, aseptic necrosis, osteoporosis, ulcers, pancreatitis, pseudotumor cerebri, psychosis, glaucoma, cataract formation, vascular necrosis, increased susceptibility to infection, impairment 35 of the hypothalamus-pituitary axis, decreased thyroid hormone serum binding proteins, and impaired wound healing.

Complications of Immunosuppression

In addition to the above listed toxicities and undesirable side effects, potent immunosuppression as required in the transplantation setting leads to prolonged immune compromise and predisposes the patient to infections (80% of the patients) and cancer (ranging between 10-40% of the patients). This risk has been proposed to result from impaired immune surveillance mechanisms, chronic antigenic stimulation, reactivation of latent oncogenic viruses and the direct oncogenic effects of the immunosuppressive agents.

Moreover, 40% of the deaths of transplant patients are attributable to the complications of infections or a combination of infection and graft rejection. The infections experienced by transplant patients are 50% bacterial, 30% viral, 15% fungal. Some of the common bacterial infections are Staphylococcus aureus, Staphylococcus epidermidis, and gram-negative rods in line sepsis. Urinary tract infections, pneumonias, wound infections, and surgical infections (including cholecystitis, appendicitis, diverticular disease, ulcer, etc.). Common viral infections include cytomegalovirus, Epstein-Barr virus, Herpes Simplex Virus, and varicella zoster virus. Further, common fungal or protozoan infections include Candida albicans, Asperigillus flavus, Cryptococcus neoformans, Coccidioides immitis, Histoplasma capsulatum, Norcardia asteroides, and Pneumocystis carinii.

#### Description of Mechanism of Action Hypotheses for Future Immunosuppressive Drug Development

The majority of the hypotheses for future therapeutic interventions for graft rejection and graft immunoreactivity are based upon the understanding the immunologic mechanisms that cause and perpetuate the rejection within the graft.

A gene, genes, or gene pathway involved in the etiology of transplantation or immunosuppression or associated disorders or potential sites for targeted drug therapy of transplantation are depicted in Table 9 with the specific gene list in Table 4. Current candidate therapeutic interventions in development for the treatment of anemia are listed in Tables 42 and 43.

#### E. Pain Associated with Inflammation

##### Description of Pain Associated with Inflammation

Pain associated with inflammation can be caused by pathologic processes in somatic structures or viscera, or by prolonged dysfunction of parts the peripheral nervous system.. Pain associated with inflammation may be the result of recurrent injuries, trauma, headache, arthritis, chronic obstructive pulmonary disease, psoriasis, or other pathologies. Pain associated with inflammation may be acute or chronic depending on the level and extent of the inflammation.

### Current therapies for Pain Associated with Inflammation

Therapeutic management of pain resulting from inflammation includes a three step ladder approach: non-opioid analgesics are stepwise prescribed in combination with moderate to potent opiates. The guidelines call for a determination by the patient and the physician of pain relief. Broadly speaking, the guidelines are as follows: mild pain is treated with non-opioid analgesics, moderate or persisting pain is treated with a weak opioid plus non-opioid analgesics, and severe pain that persists or increases is treated with a potent opioid plus non-opioid analgesics.

Analgesics: Typically, pain associated with inflammation can be controlled with NSAIDs including but not excluded to, salicylates, para-aminophenol derivatives, indole and indene derivatives, heteroaryl acetic acids, arylpropionic acids, anthranilic acids, enolic acids, or alkanones. Antiinflammatory agents such as cyclooxygenase inhibitors, lipoxygenase inhibitors, and others can be used to block the inflammation physiological pathway which mediate pain and the progression of the disease. However, because these drugs are limited in their efficacy in advanced or more severe stages of arthritis, these agents are add-on therapies.

NSAIDs derive their principle mechanism of action by the inhibition of prostaglandin and leukotriene synthesis. These compounds inhibit key enzymes in the biosynthetic pathway, i.e. cyclooxygenase. There are drugs that selectively inhibit isoforms of cyclooxygenase 1 and 2 (COX-1, COX-2) which enhances patient tolerance due to the prevalence of COX-2 induction occurs in inflammation mediated by cytokines and others.

Further, pyrimidine synthesis inhibitors can be used as an antiinflammatory agent in arthritis, e.g. leflunomide.

### Limitations of Current Therapies for Pain Associated with Inflammation

#### Limitation of Therapies for Pain Associated with Inflammation due to Low efficacy

The therapies discussed above are limited to the slowing or retarding the progression of arthritis. As degeneration of the joints progresses, and irreversible damage occurs, the options become limited. Thus, therapies for arthritis are aimed at reduction of manifestation of symptoms by controlling the clinical manifestations of inflammation.

#### Limitations of Therapies of Pain Associated with Inflammation due too Toxicity or Undesired side effects

Analgesics associated side effects include dyspepsia, gastric or small bowel bleeding, ulceration, renal insufficiency, confusion, rash, headache, hepatic toxicity. NSAIDs also reversibly inhibit platelet aggregation and prolong bleeding time.

5     Description of Mechanism of Action Hypotheses for Future Pain Associated with Inflammation Drug Development

10     The persistence of pain most likely involves a cascade of pathological neurochemical events that lead to abnormal sensory hyperexcitability and excitotoxicity. The genes listed in Figure 1 are part of a pathway are all involved in producing prostaglandins or leukotrienes, which are two potent mediators of inflammation. Inordinate levels of prostaglandins have been implicated in pain associated with inflammation, and several drugs target this branch of the pathway, to inhibit the action of leukotrienes. When a cell receives a pro-inflammatory stimulus, such as tumor necrosis factor, membrane phospholipids, or interleukin-1, as shown in 15 the figure, membrane phospholipases are activated, and arachidonic acid is released from membrane phospholipids into the cell. The liberated arachidonic acid is then metabolized either by the cyclooxygenase enzymes, which leads to the production of prostaglandins, or the lipoxgenase family of enzymes, which leads to the production of leukotrienes. There are several types of prostaglandins and leukotrienes, and many of the enzymes listed here function to convert one form into another. 20

The presence of leukotrienes and prostaglandins can lead to a persistence of neural hyperexcitability involving a sequence of neuroplastic events.

25     A gene, genes, or gene pathway involved in the etiology of pain or associated disorders or potential sites for targeted drug therapy of pain are depicted in Table 9 with the specific gene list in Table 4. Current candidate therapeutic interventions in development for the treatment of pain associated with inflammation are listed in Table 44.

30     F. Psoriasis

Description of Psoriasis

Papulosquamous skin disorders have diverse etiologies and include psoriasis, Reiter's syndrome, pityriasis rosea, lichen planus, oityriasis rubra pilaris, secondary syphilis, mycosis fungoides, and ichthyosiform eruptions.

35     Psoriasis is a genetically determined, chronic epidermal proliferative disease with an unpredicable course. Psoriasis appears as erythematous plaques with silvery, mica-like scales, and is usually nonpruritic. The plaques appear anywhere on the body and almost never involves the mucous membranes. There are variations of psoriasis including guttate psoriasis, inverse psoriasis, pustular psoriasis,

erythroderma, and psoriatic arthritis. There is an increased prevalence of psoriasis in subjects with the HLA antigens BW17, B13, and BW37. Further, 30% of cases have a family history of psoriasis. The Koebner phenomena is a hallmark characteristic of psoriasis, e.g. intense trauma (scratches or surgical incisions) to the skin induces new linear papulosquamous lesions.

This multifactorial disease is characterized by an accelerated cell cycle in an increased number of dividing cells that results in rapid epidermal cell proliferation. It is estimated that 4-5 million Americans have psoriasis, 100,000 have severe cases, and 1 in 20 have psoriatic arthritis.

#### Current Therapies for Psoriasis

The goals of the therapeutic regimens is to limit the epidermal proliferation underlying the dermal inflammation. There are both topical and systemic treatments available, however in either category the treatment suppresses the condition for only as long as is administered. The treatment of psoriasis entails a stepwise increase of extent of the therapy ranging from topical applications to phototherapy to systemic interventions to prevent the epidermal proliferation.

In the first step topical treatments include corticosteroid ointments, vitamin D containing ointments, preparations containing coal tar or anthralin, salicylic acid containing ointments, and various other moisturizers and bath solutions. These steps are aimed at reducing the itching, scaling, and progression of the lesions.

In the second step, phototherapy other than natural sunlight can be used to thwart the epidermal cell proliferation. In these cases, ultraviolet light is administered to affected areas or uniformly to the body. In phototherapy, light delivered to the skin activates porphyrin molecules. These activated molecules transfer their energy to form cytotoxic singlet oxygen leading to lethal alteration of cellular membranes and subsequent tissue destruction. In UVB therapy, UVB light is administered alone or with ointments containing coal tar, anthralin, or salicylic acid. UVA light is administered with psoralen.

In the third step of therapeutic regimens for psoriasis, systemic agents are administered to those cases refractory to the previously described first two steps. These compounds include retinoids, methotrexate, hydroxyurea, cyclosporin, azathioprine, 5-fluorouracil, cyclophosphamide, vinblastine, dapsone, and sulfasalazine.

#### Limitations of Current Therapies for Psoriasis

The main limitation of the current therapies for psoriasis is that the drugs are only efficacious during the administration. Further, periods of remission and

outbreaks are difficult to impossible to predict. It has been shown that patients must rotate their treatments to retain efficacy. This can lead to missed schedules and requires patient education. Lastly, for all the listed therapies there is unreliable efficacy in their ability to stop proliferation and inflammation of the lesions.

5           Toxicities of the current therapies include the following: phototherapy can lead to other skin lesions and sunburn. Cytotoxic agents used as immunosuppressive agents including methotrexate, 5-fluorouracil, cyclophosphamide, and vinblastine have associated side effects including hepatic compromise including hepatic fibrosis, ascites, esophageal varices, cirrhosis, pneumonitis, myelosuppression,  
10           (cyclosporine: renal insufficiency anemia, hypertension).

          A gene, genes, or gene pathway involved in the etiology of psoriasis or associated disorders or potential sites for targeted drug therapy of psoriasis are depicted in Table 9 with the specific gene list in Table 4. Current candidate therapeutic interventions in development for the treatment of psoriasis are listed in  
15           Table 45.

#### G. Atherosclerosis

##### Description and Potential Intervention of Atherosclerosis

          Atherosclerosis is a complex combination of hyperlipidemia, injury to the  
20           endothelium, and inflammation. The interaction of these multiple processes in association with local genetic and hemodynamic influences may promote the formation of atheromatous plaques as a reparative response of the arterial wall. Atherosclerotic plaques are composed of thrombogenic lipid-rich core protected by a fibrous cap comprising smooth muscle cells and inflammatory cells. The  
25           inflammatory cells are predominantly macrophages. As atherosclerotic plaques build blood flow is reduced creating ischemia in tissues down stream from the area of the plaque.

          In another model, the stenosis created by the plaques may be a part of the resulting ischemic event. Frequently, less obstructive but more vulnerable plaques  
30           occur which are characterized by a thinned fibrous cap, marked lipid accumulation, a large number of macrophages, and a smaller amount of smooth muscle cells. It has been proposed that since these plaques are more prone to rupture creating contact with the highly thrombogenic materials of the lipid-rich nucleus of these lesions, thrombosis is stimulated.

35           Advanced atherosclerotic lesions are caused by a series of cellular and molecular events involving replication of smooth muscle cells and macrophages on the vessel wall. The interaction of these cells with the T lymphocytes can lead to a fibroproliferative response. Large amounts of connective tissue produced by these

smooth muscle cells consist of macrophages, T lymphocytes, smooth muscle cells, connective tissue, necrotic residues, and varying amounts of lipids and lipoproteins.

Endothelial cells maintain the vessel surface in a non-thrombogenic state, preventing platelet and leukocyte adhesion, and act in maintaining the vascular tonus by releasing nitric oxide, prostaglandin, and endothelin. These cells also produce growth factors, cytokines, and chemokines to maintain the integrity of the collagen- and proteoglycan-rich basement membrane. Changes in some of these functions may trigger cell interactions with monocytes, platelets, smooth muscle cells, and lymphocytes. Hyperlipidemia and hypercholesterolemia are sufficient to induce dysfunction of the endothelial modulation of the vasoactive reactions and arteriolar tonus.

The inflammatory mechanisms involved in the initial events or atherosclerosis are classic components of a specialized type of chronic inflammatory response that precedes the migration and proliferation of smooth muscle cells of the vessel wall. The formation and accumulation of foam cells in the intima leads to the first stage of the atherosclerotic lesion. In this stage, the accumulation of fatty striae consisting of a mixture of macrophages, lipids, and T lymphocytes representing a purely inflammatory response. If the stimulating agent is maintained, i.e. hyperlipidemia, hypercholesterolemia, or other risk factor, then the protective inflammatory response will also persist and may become deleterious to the cells lining the arterial wall. This condition may lead to an intermediate lesion that may contain multiple smooth muscle cell layers, macrophages, and T lymphocytes. A fibrous capsule is formed covering the contents of the lesion.

There is evidence to suggest that the inflammatory process and specific immune mechanisms are involved in atherogenesis. At sites close to the plaque rupture, inflammatory processes are observed resulting from T cell-dependent autoimmune response. This may lead to inflammatory reactions participating in the destabilization of the fibrous cap. Immunoglobulins, T lymphocytes, and macrophages are found in the plaques. B lymphocytes and plasmacytes may also be detected in the adventitia adjacent to the plaques. Autoimmune reactions against the oxidized lipoproteins have been observed. The macrophages are transformed into foam cells and in the presence of LDL, form immunocomplexes with the LDL by Fc fragments of the immunoglobulins. These LDL immunocomplexes can induce numerous metabolic and functional changes which can directly or indirectly damage the endothelial cells leading to the progression of the atherosclerotic lesion.

Despite the evidence of the involvement of the immune system in atherogenesis, the complexity of the immune reactions and response impairs the clarification of the involvement of these mechanisms at the various stages of

atherosclerosis. The sequence of immune response event suggests an initial mechanism to respond to injury. However, this protective inflammatory response in the presence of persistent stimulus and the formation of a fibroproliferative response can be amplified.

5           Attempts to modify the specific cell interactions with growth factor mediators or intracellular signalling molecules has provided a window to the potential prevention or regression of the lesions.

          A gene, genes, or gene pathway involved in the etiology of atherosclerosis or associated disorders or potential sites for targeted drug therapy of atherosclerosis are depicted in Table 9 with the specific gene list in Table 4. Current candidate  
10           therapeutic interventions in development for the treatment of atherosclerosis are listed in Table 46.

#### Endocrine and Metabolic Disease

15           Included in the description below are endocrinologic and/or metabolic diseases, disorders, or syndromes. They include diabetes, diabetes insipidus, obesity, contraception (not a disease but a common reason for taking steroid drugs), infertility, hormonal insufficiency related to aging, osteoporosis, acne, alopecia, adrenal dysfunction, thyroid dysfunction, and parathyroid dysfunction. Application  
20           of the methods of this invention to these diseases is described.

##### *A. Diabetes Mellitus*

          Carbohydrate metabolism in mammals is controlled by a unique interplay of hormones, neurotransmitters, and other physiological influences to ensure a constant  
25           supply of metabolic fuel is available to the tissues. The two main hormones that regulate carbohydrate balance are insulin and glucagon. Both hormones are produced in the pancreas;  $\beta$ -cells produce insulin,  $\alpha$ -cells produce glucagon. Insulin in the fuel excess state stimulates storage of the available metabolic precursors into glycogen and lipids; glucagon in the fuel deficient state stimulates the movement of  
30           the fuel stores to available metabolic precursors. When regulation of insulin or glucagon is abnormal there are pathologic changes.

          Type II Diabetes (Diabetes Mellitus; DM) is a heterogeneous disorder of carbohydrate metabolism characterized by absolute or relative insulin deficiency alone or in combination with insulin resistance (sensitivity). DM is associated with  
35           hyperglycemia and consequent polyuria and polydipsia.

          There are two forms of the disease, insulin-dependent diabetes mellitus (IDDM) which accounts for approximately 10% of the DM cases in the United States, and non-insulin-dependent diabetes mellitus (NIDDM) which accounts for



the remaining diagnosed cases. The incidence rate for all cases of DM in the U.S. is approximately 440 per 100,000. Type I (juvenile onset) diabetics produce little or no insulin and may be severely hyperglycemic if untreated. They are entirely dependent on exogenous insulin administration.. NIDDM (maturity or adult onset, nonketotic DM) patients retain significant capacity to secrete insulin, do not exhibit ketosis, and are not dependent on exogenous insulin for immediate survival. Within the pancreas, the  $\beta$ -islets cells are lost, stop producing or secreting insulin in patients with IDDM, but remain functional in patients with early stage NIDDM. In both cases of DM, glucagon opposes the effect of insulin on the liver by stimulating glycogenolysis and gluconeogenesis, but glucagon has little if no effect on the peripheral utilization of glucose. In the diabetic patient with insulin deficiency or insulin resistance and hyperglucagonemia, there is an increase in hepatic glucose production, a decrease of peripheral glucose uptake, and a decrease in the conversion of glucose to glycogen in the liver.

Broadly, the physiologic changes stimulated by insulin, the primary hormone responsible for specific uptake of glucose from the periphery to tissues, is to increase the available storage of glucose into glycogen stores. In the liver, insulin stimulates the uptake and storage of glucose as glycogen, and inhibits hepatic gluconeogenesis and glycogenolysis. In skeletal muscle, insulin stimulates glucose uptake and storage as glycogen and amino acids in protein and inhibits release of gluconeogenic precursors (e.g., alanine, lactate and pyruvate) to the hepatic circulation. In adipose tissue, insulin stimulates the glucose uptake and metabolism to glycerol (the backbone of triglycerides for storage in fat droplets) and inhibits the flow of gluconeogenic precursors to the hepatic circulation, e.g. glycerol and nonesterified fatty acids. Insulin inhibits the breakdown of triglycerides, glycogen, protein and the conversion of amino acids to glucose (gluconeogenesis).

In the intracellular process of storage of glucose as glycogen in the liver, insulin stimulates the glycogen synthase complex and inhibits glycogenolysis. However, in the insulin deficient or insulin resistant patient, glycogen stores are depleted and replaced with stores of ketone bodies (see below).

In the intracellular process of storage of amino acids in muscle as protein, insulin stimulates the production of amino acids and their incorporation into protein. In the absence of insulin, the amino acids stored in the muscle or other tissues, protein manufacture is reduced, and all available amino acids are metabolized to pyruvate, oxaloacetate, and  $\beta$ -ketoglutarate. The pyruvate can be converted to acetyl-CoA which can be further metabolized to acetoacetate, free fatty acid-CoA, or enter the cholesterol synthetic pathway via HMG CoA. In this case, there is production of ketones, fatty acids, and cholesterol.

In the intracellular process of storage of metabolic fuel within the adipose tissue, insulin stimulates lipoprotein lipase. Lipoprotein lipase is synthesized primarily in fat and muscle, and when secreted into the extracellular space, the enzyme is associated with the surface of endothelial cells. Lipoprotein lipase hydrolyzes free fatty acids from triglyceride-rich lipoproteins (i.e. chylomicrons, very low density lipoproteins). Free fatty acids liberated from the lipoproteins are then taken up by adipose tissue, esterified into triglycerides for storage in fat droplets or adipocytes. Insulin stimulates the synthesis and secretion of lipoprotein lipase, inhibits lipolysis of triglycerides stored in adipose tissue, and promotes glucose uptake into the fat stores to provide a glycerol substrate within the adipocytes for esterification of the fatty acids.

In cases whereby there is limited insulin supply or responsivity, there is an enhanced production of free fatty acids. The excess of free fatty acids stimulates the production of ketones ( $\beta$ -hydroxybutyrate, acetoacetate) and the release of ATP. Diabetic ketoacidosis (DKA) describes a clinical situation whereby there is a severe elevation of ketones in the tissues and peripheral circulation with concomitant hyperglycemia. In hepatocytes, mitochondria produce ketone bodies, which form as the result of  $\beta$ -oxidation of fatty acids. Glucagon further stimulates the hepatic ketogenic state; glucagon lowers malonyl coenzyme A levels (the first enzymatic step in the production of fatty acids) which in turn stimulates the activity of carnitine acyltransferase I, an enzyme that translocates fatty acids from cytosolic to intramitochondrial spaces. The fatty acids once in the mitochondria are converted in the absence of glucose to ketones.

The production of excess ketones in DKA is uncontrolled: normally insulin stimulates the ketoacid tissue uptake and the high concentration of ketones themselves saturates tissue uptake. However, in DKA, the only resultant mechanism to remove or excrete excess ketones is via the kidneys. Hyperketonuria causes osmotic diuresis, which in turn causes intravascular volume depletion and dehydration, leading to urinary electrolyte loss. The hyperosmolarity exaggerates the intracellular dehydration.

The hallmark of NIDDM is peripheral tissue insulin resistance. The characteristic post-insulin receptor defect has been difficult to target therapeutically, however, there are working hypotheses to be exploited during drug development. One theory to explain how insulin resistance comes about is the single gateway theory. In the liver, it is thought that insulin is acting not directly on the hepatocytes, but through an indirect means. In this theory, insulin resistant fat cells over produce free fatty acids. It is the free fatty acids that circulate to the liver,

muscle, and others tissues to mediate insulin resistance by a yet unknown mechanism of action.

Another explanation of insulin resistance is free fatty acid response within adipose tissue. In this theory, free fatty acids stimulate the adipocyte production of TNF $\alpha$  and TNF $\alpha$  creates insulin resistance locally and distally within other peripheral tissues. It is thought that TNF $\alpha$  mediates insulin resistance within adipose tissues by stimulating de-differentiation by inhibiting peroxisome proliferator receptor- $\gamma$  (PPR- $\gamma$ ) and CAAT-enhancer binding protein  $\alpha$  (CEBP $\alpha$ ) while activating serine-threonine phosphorylation via the MAP kinase cascade. TNF $\alpha$  has been shown to stimulate lipolysis. Further, TNF $\alpha$  stimulates apoptotic signals by activating capases. Within the skeletal muscle TNF $\alpha$  inhibits insulin stimulated glucose uptake, and directly affects the insulin signaling pathway; it stimulates phosphorylation of the IRS-1; and inhibits PPR- $\gamma$  and CEBP $\alpha$ . An example of the importance of TNF $\alpha$  on the mediation of insulin resistance are recent studies in adipocyte macrophages whereby it has been shown that TNF $\alpha$  has a direct effect on macrophages metabolism (a shift from glucose utilization to free fatty acid production) and a direct effect on PPR- $\gamma$  and CEBP $\alpha$ .

Type II DM is associated with metabolic syndrome X, also referred to as insulin resistance syndrome, or metabolic syndrome. This syndrome is characterized by hypertriglyceridemia, low serum high density lipoprotein (HDL) and cholesterol, hypertension, central obesity, defective fibrinolysis, and arteriosclerosis. Syndrome X, "the deadly quartet" of obesity, NIDDM, hypertension, and dyslipidemia are common metabolic disorders that have been shown to predispose the patient to early cardiovascular disease, including but not limited to coronary artery disease, heart failure, or congestive heart failure. In these cases, the pancreatic  $\beta$ -cells produce insulin, but the peripheral tissues are physiologically unresponsive to insulin. Thus, the mechanisms of insulin deficiency are active and the resultant hyperglycemia, hyperlipidemia, and others described are present. Clinically, the patient exhibits the signs and symptoms of NIDDM, and unfortunately few therapeutic alternatives are available. Table 50 lists the current candidate therapeutic interventions that are in development for the treatment of IDDM and NIDDM.

*Metabolic Syndrome X-* It is well known that individuals who are diagnosed with metabolic syndrome X progress to a diagnosis of IDDM. One explanation of the transition of insulin independent to insulin dependent DM is that the overactive, uncontrolled pancreatic  $\beta$ -cells in NIDDM may generate oxygen free radicals that are deleterious to the  $\beta$ -cells and they undergo apoptosis. Another theory that may explain the loss of  $\beta$ -cells is that free fatty acids produced in adipose, hepatic, and

other tissues may compromise the activity of the functioning pancreatic  $\beta$ -cells and ultimately leads to  $\beta$ -cell apoptosis and death. Lastly, the overexpression of TNF $\alpha$  within adipose tissue may activate apoptotic signals within the pancreatic  $\beta$ -cells.

Therefore, in cases of NIDDM, it is clinically advantageous to blunt the progression of the disease to syndrome X. Therapeutic alternatives to treat NIDDM are as follows: 1) diet modifications that are aimed at lowering the daily intake of glucose (carbohydrates) and lipids; 2) low doses of exogenous insulin can be used to inhibit the patient's production and secretion of insulin from the pancreatic  $\beta$ -cells; 3) oral hypoglycemic agents, e.g. sulfonylureas (first and second generations), biguanides, thiazolidinediones, and  $\alpha$ -glucosidase inhibitors. Once in syndrome X, there are many other therapeutic alternatives that are added to the regimen to treat the "deadly quartet" as described above.

Novel therapeutic alternatives are required to be developed to meet the need of the population of NIDDM as well as those individuals in which progression to syndrome X has occurred. Table 56 lists the current candidate therapeutic interventions in development for the treatment of one or more of the deadly quartet that is part of metabolic syndrome X.

Many human primary and metastatic tumors express critical proteins required for the maintenance of growth and dedifferentiation along with proteins that may inhibit growth or enhance terminal differentiation. For example, breast adenocarcinomas express at significant levels peroxisome proliferator activated receptor gamma (PPAR $\gamma$ ), that when activated by a specific ligand, will induce terminal differentiation of malignant breast epithelial cells. Although, specific activators of PPAR $\gamma$  have been developed for the treatment of NIDDM, the antiproliferative and terminal differentiation effect may be exploited for the development of anti-neoplastic agents. Further, agents affecting the PPAR $\gamma$  pathway may be desirable candidate therapeutic interventions for cancer and DM. Current candidate therapeutic interventions for the treatment of cancer are listed in Table 24.

Besides metabolic syndrome X, there are other chronic late complications of IDDM and NIDDM including retinopathy (proliferative and nonproliferative), nephropathy, neuropathy (including symmetric distal polyneuropathy, asymmetric neuropathy, cranial mononeuropathy and mononeuropathy multiplex), peripheral mononeuropathy and, neuromuscular syndromes and autonomic neuropathy, cardiovascular disease, and skin ulcers due to vascular disease. In cases with loss of sensation in the extremities, there is a predisposition to repeated and undetected trauma. Diabetics are also at increased risk for cardiovascular disease. These complications are only partially reduced by achieving tight control of blood glucose levels.

### *B. Diabetes Insipidus*

The polyuric syndrome in which there is a dysfunction in the antidiuretic hormone (ADH, often referred to as vasopressin (AVP)) signalling pathway, with an loss of ADH activity, and is termed diabetes insipidus (DI). Since ADH is responsible for the appropriate concentration and water conservation in the body, clinical manifestations of this disorder include: polyuria, near-continuous thirst, nocturia, hypertonic encephalopathy, circulatory collapse, and hypernatremia. These symptoms can lead to life-threatening syndromes.

In DI, there is a vasopressinergic deficiency or the target organs are unresponsive to ADH (nephrogenic diabetes insipidus). The etiology of the disorder includes disease processes of the supraoptic nuclei, paraventricular nuclei, the hypothalamohypophyseal tract, or the pituitary gland. Although 30% of the cases are attributed to neoplastic lesions of the hypothalamus, 30% are post-traumatic, and 30% are idiopathic, with the remaining 10% being attributed to vascular lesions, infections, systemic diseases such as sarcoidosis that affect the hypothalamic function, and mutations in the ADH gene preprohormone processing pathway.

Treatment of DI depends on the level and extent of the vasopressinergic deficiency. In cases, restoration of fluid balance and control of dehydration is paramount. In some cases of partial loss of ADH, relief of symptoms can be attained through the use of vasopressinergic agonists, candidate therapeutic interventions that enhance vasopressin secretion (e.g. clofibrate), or agents that increase the renal response to vasopressin (e.g. chlorpropamide).

In cases of nephrogenic DI, there is an inability of the renal cells to respond to vasopressin. In one form of this condition, there is congenital defects of the vasopressinergic receptor V2, preventing the ADH stimulation of adenylate cyclase and is an X-linked autosomal dominant genetic condition. In another form of nephrogenic DI, there are mutations in the autosomal gene for aquaporin-2 which produce a nonfunctional versions of this water channel.

Although DI is more common, hypersecretion or over-activity of the ADH pathway leads to a syndrome termed inappropriate hypersecretion of ADH (SIADH). In this syndrome there is profound hyponatremia. This syndrome can occur in patients with cerebral disease (cerebral salt wasting) or pulmonary disease (pulmonary salt wasting), in some cases whereby a tumor is hypersecreting vasopressin, or in the absence of complicating disease. In these cases, patients with inappropriate hypersecretion or vasopressin can be successfully treated with agents or candidate therapeutic interventions that interrupt the vasopressinergic signal, for example, meclocycline, an antibiotic that reduces the renal response to vasopressin.

### C. Obesity

According to a commonly accepted definition, obesity refers to a condition by which more than 20% or 25% of body weight is due to fat in men and women, respectively. Another, more reliable, index of fat distribution is the body mass index (BMI) which is calculated as the body weight divided by the square of the height (normal range being 20-25 kg/m<sup>2</sup>). Obesity is a serious illness that can lead to many complications including hypertension, diabetes, cancer, degenerative arthritis, elevated cholesterol, gallstones or inhibited bile secretion, heart attacks and other cardiovascular disease, strokes, sleep disorders, and psychiatric illnesses including anxiety and depression. There is a strong genetic component to obesity, as well as strong correlations between obesity and socioeconomic status.

Tables 5 and 10 lists the possible genes and gene pathways involved in the manifestation of obesity. Specifically, there are two gene pathways that may be associated with a genetic predisposition to obesity, they are leptin and its receptor, and peroxisome-proliferator-activated receptor  $\gamma$ 2 (PPAR $\gamma$ 2). In the first, the lipostatic hypothesis of obesity achieved prominence for a potential mechanism of inordinate eating. It was determined in mice lacking a specific gene, the *ob* gene, did not become sated after eating and ultimately became obese and diabetic. The product of this gene is a 167 amino acid protein called leptin. Leptin acts as a hormone to reduce food intake and increase energy consumption. The leptin receptor is encoded by the *db* gene. Mice lacking the *db* gene are also obese, but have high levels of circulating leptin. The leptin receptor is found in two forms, the short and long form which are the result of alternative splicing. The long form is found in the hypothalamus.

The mechanism of leptin and leptin receptor dysfunction creating obesity is thought to occur by (i) interfering with the transport of leptin into the ENDOCRINE AND METABOLIC, (ii) impairing leptin receptor signal transduction, (iii) impairing downstream mediators of leptin action, or (iv) causing obesity by a leptin-independent mechanism – for example a mechanism that originates downstream of leptin or that bypasses leptin. Each of these hypotheses invokes a set of candidate genes (with considerable overlap) and implies up or down variation in allele function.

The genes with potential affect on leptin and leptin associated activity are leptin receptor (OB-R), melanocortin 4-receptor (MC4-R), pro-opiomelanocortin (POMC; the precursor of  $\alpha$ -melanocyte stimulating hormone), and prohormone convertase 1 (PC1). Two lines of evidence suggest that variation in these genes may affect leptin resistance. First, each gene has been strongly implicated in the leptin

signaling pathway by *in vitro* data. Specifically, PC1 participates in the processing of the prohormone POMC to the  $\alpha$ -melanocyte stimulating hormone ( $\alpha$ -MSH), which signals decreased food intake in response to leptin. This signal is transmitted through MC4-R, the receptor for  $\alpha$ -MSH. Second, mutations in each of these genes have been associated with obesity in humans and, except PC1, in rodents as well. Leptin signaling could be affected by polymorphisms that affect protein levels or function. Furthermore, there may be polymorphisms in the promoters of all four genes as well as the genomic locus of the leptin receptor and three genes implicated in the signal transduction pathway immediately downstream of the leptin receptor.

Other genes involved in the leptin signal include Neuropeptide Y. Each gene in this set has the potential to modulate the biological function of leptin. Neuropeptide Y, which stimulates food intake through the Y1 and Y5 receptors (and possibly others), is inhibited by leptin. Agouti-related protein inhibits MC4-R signaling and is also down-regulated by leptin. Like NPY, the melanin-concentrating hormone has been shown to stimulate feeding. These genes differ from those above in that mutations have not been associated with obesity in humans (although mutations in the neuropeptide Y1 receptor and the agouti-related protein have been associated with obesity in rodents). With the exception of neuropeptide Y (NPY), where the coding region (but not genomic or promoter sequence) has been screened for polymorphism, these genes have not been studied extensively for variation in humans.

In the second gene pathway associated with obesity, PPAR- $\gamma$ 2, is a transcription factor (described above and in Example 1) and has been demonstrated to be a key regulator of adipocyte differentiation and energy storage. PPAR- $\gamma$ 2 is involved in the direction of differentiation of preadipocytes to adipocytes. In *in vitro* studies, over expression of PPAR- $\gamma$ 2 leads the fibroblast cells to differentiate to adipocytes. Furthermore, phosphorylation of PPAR- $\gamma$ 2 at a serine residue at position 114 reduces differentiation process mediated by PPAR- $\gamma$ 2. This serine is contained within a mitogen activated protein kinase or related kinase, indicating an intracellular mechanism for the regulated control of adipocyte differentiation. In a recent study, it was determined that 4 of 121 obese subjects were identified as harboring a substitution of proline to a glutamine at amino acid position 115 as compared to none of the normal subjects having the substitution (Ristow et al, NEJM 339(14):953-959). Since the amino acid at position 115 is near to the serine phosphorylation site at 114, it is suggestive that such a substitution can be predisposing to aberrant PPAR- $\gamma$ 2 activity.

Other genes that be involved in the genetic differences in obese versus normal weight subjects include signaling genes based on two observations. First,

although no human or rodent models are available to assess the affect of mutation on body mass, it has been shown that JAK2 and STAT3 knockouts are embryonic lethals. This would seem to indicate functions beyond regulation of body mass. Second, there is considerable redundancy in most signal transduction pathways, and there may be compensatory mechanisms to overcome any effects of polymorphism in JAK2 or STAT.

As depicted in Table 51, there are many new candidate therapeutic interventions in development. The targets include galanin,  $\beta$ 3-adrenergic receptor, neuropeptide Y, corticotropin releasing factor, and the cholecystokinin receptors.

#### *D. Contraception*

The most widely used oral contraceptives are estrogens and progestins alone or in combination. These agents are taken by women each day to prevent ovulation. The combination therapies are either mono-, bi-, or triphasic which are named as such to indicate the level of estrogen in each of the tablets, i.e. monophasic has the same amount, biphasic has two different doses, and triphasic has three. Progestins are delivered in the same tablet, and the ratio of estrogen to progestin allows for a reduction in the overall amount of steroids delivered to the subject as well as more closely approximates the natural steroid ratio during a menstrual period. The phase delivery of steroids to women wishing to block ovulation has limited the untoward side-effects progestins have on the cardiovascular system.

Unfortunately, although very effective, oral contraceptives are associated with undesirable side effects and toxicity. These effects falls into three categories: cardiovascular effects, cancer, and metabolic and endocrinologic effects.

Cardiovascular effects seen in response to oral contraceptives include estrogen increasing serum HDL while lowering serum LDL and progestins decreasing HDL and increasing LDL. This inordinate and unregulated change in the liporpotien balance in women can lead to hypertension.

Estrogen is a growth promoting hormone, and the estrogen found in almost all of the oral contraceptives has been studied for effects on or risk of ovarian, cervical, endometiral, and breast cancer as well as hepatocellular adenoma in women. However, studies have not conclusively demonstrated an association of higher rates of these types of cancers in women that have used oral contraception.

The metabolic and endocrine effects of oral contraceptives are increased fasting glucose levels, peripheral insulin resistance, higher incidence of gall bladder disease, and estrogen mediated increases of hepatic synthesis of serum proteins.

There are other side effects and disease risk that are associated with oral contraceptives that include increased risk of thromboembolism, nausea, vomiting,



dizziness, headaches, decreased libido, visual disturbances, depression, and post-pill amenorrhea. However, there are beneficial effects of oral contraceptives that include reduction of pelvic inflammatory disease, lower incidence of iron deficient anemia, symptomatic relief of endometriosis, improvement of acne and  
5 dysmenorrhea, as well as decreased risk to develop ectopic pregnancies, uterine fibroids, and ovarian cysts.

Oral steroid contraceptives also interact with several other drugs and such interactions can lead to loss of efficacy and include altered drug absorption or metabolism. Any agent or compound that induces hepatic microsomal enzymes or  
10 reduces the absorption can alter the effectiveness of the oral contraceptives and these include certain antibiotics, anticonvulsants, or antacids. Furthermore, agents that oppose the therapeutic effects of the oral contraceptives include anticoagulants, antidiabetics, and certain antihypertensives (guanethidine, and  $\alpha$ -methyldopa).

There are other genes that one may correlate to candidate therapeutic  
15 responses or safety and these include: blockade of implantation, blockade of sperm penetration into the egg, or blockade of sperm production.

As depicted in Table 52, there are many candidate therapeutic interventions that are currently in development to be of therapeutic benefit in contraception.

#### 20 *E. Infertility*

Infertility is the involuntary inability to conceive a child. Infertility is the result of one or more of the following functions for the male or female including 1) adequate production of normal motile sperm, 2) ejaculation of sperm through a patent ductal system, 3) the sperm must be able to traverse an unobstructed female  
25 reproductive tract, 4) the female must ovulate and release the ovum, 5) the sperm must be able to enter the ovum, 6) the fertilized ovum must be capable of developing and implanting in the appropriately prepared endometrium. Nearly 40% of the infertility cases, the male has a dysfunction or inadequate function.

Couples experiencing infertility have alternatives to alter their reproductive  
30 capacity. Although many of the methods are mechanical and require a procedure, such as *in vitro* fertilization and sperm collection and concentration, there are agents that help a female to ovulate, such as antiestrogens and gonadotropins.

#### *F. Hormonal insufficiency related to aging*

35 As individuals age, their androgen and estrogen levels decrease. In some cases, estrogen and androgen replacement therapy has been useful to replenish the deficiency and restore the steroid hormone stasis. In these cases, the deficiency may be the result of a loss of the receptor affinity for the ligand, loss of the receptor

levels, reduction in the production of the steroids, or increased metabolic rates of these steroids. As the aging process continues, there may be a natural reduction in the function within the estrogen or androgen target tissues.

### 5     *G. Osteoporosis*

The condition in which there is bone matrix and mineral loss is termed osteoporosis. The loss of both of these components in bone results in the reduction of strength, and increased incidence of fractures and is characterized by a net excess loss of bone resorption over bone formation. Although there are multiple causes, the most common is involutional osteoporosis which is associated with advancing age and menopause. Osteoporosis can also occur as a result of long periods of immobilization, space flight, parathyroid hormone and vitamin D deficiency, as well as in patients with excess glucocorticoids (Cushing's syndrome, or administration of glucocorticoids for the therapy of autoimmune disease, transplantation, inflammatory diseases, arthritis, asthma, Crohn's disease, atherosclerosis, or infections with potent inflammatory responses such as hepatitis).

In osteoporosis accelerated normal bone loss can be reversed by estrogens. Estrogens inhibit the secretion of IL-1, IL-6, and TNF $\alpha$ . These cytokines enhance the production of osteoclasts, and in addition, estrogen inhibits the production of TGF- $\beta$  which is thought to mediate the apoptotic signal within osteoclasts. Although estrogen can reverse bone loss in patients with osteoporosis, the doses of estrogen required are associated with higher risk of myocardial infarctions, stroke, breast and endometrial cancers. However, as described above (under *Contraception*), estrogen in lower doses and given with progestins can be of therapeutic benefit for osteoporosis and have a reduced toxicity profile.

Table 53 lists the current candidate therapeutic interventions that are in development for osteoporosis.

### 30     *H. Acne*

The most common form of noninfectious pustular skin disease is acne. It is an inflammatory skin condition affecting the pilosebaceous units and therefore is predominantly found on the face and upper trunk. Several factors can play a role in the progression of acne including 1) androgenic stimulation of the sebaceous glands, and 2) abnormal keratinization and impaction in the pilosebaceous canals causing obstruction of the sebum flow, and 3) proliferation of anaerobic bacteria. Aggravating factors such as oil-based cosmetics, and certain drugs (androgenic hormones, antiepileptics, progestins (as in oral contraceptives), systemic corticosteroids, and iodide and bromide containing agents. There are also endocrine

conditions whereby there is a hypersecretion of androgen, e.g. polycystic ovarian disease, ovarian tumors, or enzymatic hyperactivity for the production of androgens or reduced metabolism of androgens.

5 Treatment of acne is aimed at one or more of these three causes: topical agents that remove the comedones such as benzoyl peroxide, topical vitamin A preparations enhancing flow of sebum to the surface, and oral 13-*cis*-retinoic acid can decrease sebaceous gland secretion and gland size. Oral vitamin A preparations are known teratogens and should be avoided in patients who are or plan to become pregnant.

10 Table 54 lists some current candidate therapeutic interventions in development for the treatment of acne and related skin disorders.

#### I. Alopecia

Under normal conditions, scalp hair grows between 10-15mm each month. Under normal conditions, 80-85% of hair follicles are in the growing anagen stage, and 15-20% are in the dormant or telogen stage. There are multiple factors that affect the transition of the active to dormant stages and vice versa as well as factors that can affect the rate of growth and condition of hair, including physical, chemical, and emotional events. If severe conditions exists, hair growth can completely stop leading to local or wide spread hair loss. There are two types of hair loss, nonscarring (reversible) and scarring (irreversible).

20 Nonscarring or localized hair loss includes alopecia areata, tinea capitis, trichotillomania, androgenic alopecia, or traction alopecia. Localized hair loss is characterized by well-circumscribed, round, or oval patches of nonscarring hair loss which usually occurs on the scalp, eyelashes, or eyebrows. Patterns and location of hair loss can define whether there is a poor prognosis for return of hair growth.

25 Alopecia areata may be autoimmune disease and is associated with cases of Hashimoto's thyroiditis, and pernicious anemia; alopecia areata is treated with glucocorticoid topical preparations. Tinea capitis is a an infection predominantly with *Trichophyton tonsurans* and is treated with griseofulvin. Trichotillomania is a disorder referring to traumatic, self-induced alopecia and usually results from persistent twisting, rubbing and pulling resulting in localized hair loss and is treated with emotional or psychiatric therapy. Androgenic alopecia is the familiar male pattern baldness that occurs slowly as a thinning of the hair shafts and eventual loss. Androgenic alopecia is genetically predetermined and is dependent on androgens. 35 Traction alopecia occurs in subjects that over use or abuse hair styling, curling, or other traumatic devices or procedures that damage hair to the extent of hair loss. Hair loss can be further associated with secondary syphilis.

Diffuse or generalized hair loss can occur as a result of a disruption of the normal hair growth cycle. In these cases, full loss of scalp hair may be caused by severe psychological or emotional stress, systemic illness, major surgery with general anesthesia, amphetamines,  $\beta$ -blockers, lithium, probenecid, pregnancy, or discontinuation of oral contraceptives. Disruption of the anagen phase via one or more of these hair growth toxicities may weaken the hair shaft and hair breaks easily. For example, cytotoxic cancer chemotherapeutic agents and radiotherapy to the scalp affect the anagen hair growth phase. Retinoids and hypervitaminosis interferes with the keratinization of the the hair shaft. Diffuse hair loss may occur in cases of hyperthyroidism and nutritional deficiency.

Seborrheic dermatitis appears as erythema and yellow greasy scales throughout the scalp may be associated with mild diffuse hair loss.

Lastly, scarring alopecia may be the result of systemic lupu erythmatosus, discoid lupus erythmatosus, morphea, and aplasia cutis.

In all cases of alopecia, removal or cessation of trauma, agents or procedures that are damaging to the hair follicles or shafts is the first line of therapy. Further, glucocorticoids topical agents can be used to reduce inflammatory or autoimmune components of the localized or diffuse hair loss. Topical Minoxidil, for the treatment of male pattern baldness, has shown to effective in only 30% of the cases.

The androgen receptor is encoded by a gene that is known to have a region of polyglutamine repeats (encoded by CAG repeats) in the amino terminal that is responsible for transcriptional activation. In humans, the number of these CAG repeats is polymorphic. Since androgens can be important in acne, hirsutism, and androgenetic alopecia (AGA), a recent study set out to determine whether these polymorphic repeats were associated with the signs and symptoms of these clinical disorders (Sawaya and Shalita, J Cutan Med Surg 3(1):9-15, 1998). The investigators found that normal subjects had a mean of  $22 \pm 4$  ( $n=48$ ) and  $21 \pm 3$  ( $n=60$ ) CAG repeats in this region of their androgen receptor for men and women, respectively. In contrast, men with AGA had  $19 \pm 3$  and women with AGA had  $17 \pm 3$  CAG repeats. These data are suggestive that CAG repeat length found in a physiologic relevant site in the androgen receptor may be indicative of the role androgens play bin the mediation of adrogenentic alopecia.

Table 55 lists the current agents, drugs, or candidate therapeutic interventions that are in development of the therapy of alopecia.

### *J. Adrenal dysfunction*

The major function of the adrenal cortex is to produce glucocorticoids (cortisol) and mineralocorticoids (aldosterone). Either an excess or deficiency in

adrenal cortical hormones can have major physiologic effects. Cortisol is responsible for the regulation of carbohydrate metabolism, intermediate metabolism, hemodynamic functions, and developmental processes. Excess cortisol is termed Cushing's disease and cortisol deficiency is termed Addison's disease. Aldosterone is a hormone primarily involved in the regulation sodium, potassium, and hydrogen ion balance and secondarily in the regulation of blood pressure. Hyperaldosteronism or hypoaldosteronism are the terms for excess or deficiency of aldosterone. Besides cortisol and aldosterone, there are many other steroids produced in the adrenal cortex; in females the adrenal cortex is the major source of androgens.

The biosynthetic steps for the production of steroids compounds in the adrenal cortex proceeds via a series of enzymatic steps, the first molecule to enter the cycle is cholesterol, intermediates steroids (including DHEA sulfate, 17 $\alpha$ -OH-progesterone, 11-deoxycortisone, testosterone, androstenediones, deoxycortisols, corticosterones), and final products estradiol-17 $\beta$ (E<sub>2</sub>), estrone (E<sub>1</sub>), cortisol, and aldosterone. Under normal condtions, cortisol is the major end-product with aldosterone next, and very little estradiol or estrone.

Adrenal cortical steroids are secreted in repsonse to adrenocorticotropic hormone that is secreted from the pituitary in response to stimulation by corticotropin releasing hormone secreted by the hypothalamus. There is a negative feed back loop, in that cortisol inhibits the secretion of ACTH and CRH at the pituitary and the hypothalamus, as well as somatostatin acting in the same manner as cortisol to attnetuate secretion of the hypothalamus and pituitary hormones.

Once secreted, cortisol is approximately 90-93% bound by plasma proteins; albumin and the major protein being corticosteroid binding protein (CBG, transcortin). CBG has a high affinity for cortisol and is not required for transport, nor cortisol function. CBG is produced in the liver and the concentrations found in plasma is genetically determined and is regulated by hormone levels. CBG levels are increased during certain physiological conditions including pregnancy, hyperthyroidism, diabetes, in excess estrogen, and during the administration of oral contraceptives. CBG levels can be low or deficient during periods of malnutrition, in liver disease, multiple myeloma, obesity, hypothyroidism, and part of the nephrotic syndrome. In cases whereby there is an increase or decrease in the levels of CBG, bound cortisol levels increase or decrease, respectively, however there is a constant level of free cortisol. Mineralocorticoids, once secreted, are approximately 60% bound to plasma albumin.

Nearly 99% of the adrenal cortical steroids are metabolized prior to excretion. Thus, any defect or dysfunction in the enzymes involved or in the metabolic rates can result in elevated levels of cortisol or active metabolites.

Further, metabolic enzymatic reactions occur to ensure that products are sufficiently different to not elicit a biological effect in the metabolizing organ. For example, the 11 $\beta$ -hydroxyl group of cortisol can be metabolized in the liver to the ketone form which is devoid of cortisol receptor binding activity. Conversely, cortisol in the kidney can be metabolized to cortisone which prevents cortisol from binding to the mineralocorticoid receptor in the kidney. Cortisol and aldosterone are cleared from the plasma with a half-lives of 80-120 minutes and 15 minutes, respectively. The changes of metabolic rates can occur via 1) inhibitory influences of plasma binding on clearance rates. 2) enhanced metabolic enzymatic activity. The metabolism of these steroid hormones can be altered by: 1) decreased metabolism, or 2) increased metabolism. Glycyrrhetic acid, present in licorice, and carbenoxolone block the 11 $\beta$ -hydroxysteroid dehydrogenase activity and thereby prevent the conversion of cortisol to cortisone. Thus alterations as described above can lead to enhanced or decreased adrenal cortical steroid hormone activity and physiologic response.

Nearly 80% of the primary adrenocortical insufficiency cases are due to autoimmune destruction of the adrenal cortical tissue. Autoimmune adrenocortical insufficiency has some genetic predisposition; 40% of the cases have first or second degree relatives with similar clinical patterns. Nearly all the cases of secondary adrenocortical insufficiency is the result of limited secretion of ACTH.

Therapy of adrenocortical insufficiency is treated in the acute setting with intravenous soluble steroids and control of fluid and electrolyte balance. For the maintenance of cortisol levels, these patients are put on a schedule of cortisol administrations that mimic the normal physiologic circadian rhythm.

Hypersecretion of cortisol is termed Cushing's syndrome may be caused by adenocortical tumors hypersecreting cortisol, conditions that increase ACTH secretion, and by prolonged administration of corticosteroids. This syndrome is characterized by a moon face, increased fat pads, red cheeks, protuberant abdomen, abdominal striae, poor muscle development, poor wound healing, and bruisability with ecchymoses. Therapy of Cushing's syndrome is dependent on the etiology of the disease. Adrenocortical and pituitary tumors can be surgically removed, however in each case disruption of normal glandular function must be avoided. Bilateral removal of adrenal glands can lead to Nelson's syndrome which is thought to arise due to the loss of cortisol negative feedback on the pituitary gland. In the absence of tumors, drugs may be used to limit the secretion of ACTH or cortisol

they include: reserpine, bromocriptine, cyproheptadine, and valproate sodium can be used to reduce the secretion of ACTH, however only a minority of patients respond. Ketoconazole inhibits cortisol secretion.

Cortisol and the many synthetic congeners are the mainstay drug or therapy for many inflammatory diseases, conditions, or disorders and in the transplantation setting. Corticosteroids affect the immune response by decreasing growth and development of mast cells, inducing apoptosis, suppressing lymphocyte generation of IL-5 and other cytokines, inhibiting some mediator release, inhibiting cytokine production, inhibiting the transcription of cytokines (for example IL-8, TNF- $\alpha$ , prototypic antiviral chemokine (regulated-on-activation normal T-expressed and secreted, RANTES), and GM-CSF), and inhibiting nitric oxide synthesis. As well as providing antiinflammatory therapy, corticosteroids suppress immune function by inhibiting the activation of T cells. Steroids are highly effective in the early induction and maintenance regimens and are first line therapy in acute allograft rejection.

Glucocorticoid associated side effects include increased appetite, weight gain, fluid retention, acne, ecchymosis, development of cushoid facies, hypertension, hyperkalemia, diabetes, hyperglycemia, hyperosmolar state, hyperlipidemia, hepatic steatosis, atherosclerosis, myopathy, aseptic necrosis, osteoporosis, ulcers, pancreatitis, pseudotumor cerebri, psychosis, glaucoma, cataract formation, vascular necrosis, increased susceptibility to infection, impairment of the hypothalamus-pituitary axis, decreased thyroid hormone serum binding proteins, and impaired wound healing.

Mineralocorticoid hypersecretion occurs due to adrenocortical adenoma, bilateral adrenocortical hyperplasia, and adrenal carcinoma. Clinically, the symptoms include hypertension, suppression of plasma renin, hypokalemia and associated disorders or syndromes related to each of these dysfunctions. Therapy for these conditions usually entails uni- or bilateral surgical removal of the adrenal adenoma or hyperplasia. In these cases, cortisol maintenance therapy is initiated as described above.

Mineralocorticoid hyposecretion is treated with supplemental mineralocorticoid therapy.

#### K. *Thyroid dysfunction*

The thyroid gland secretes thyroxine (3, 5, 3', 5'-tetraiodothyronine, T<sub>4</sub>) and 3, 5, 3'-triiodothyronine (T<sub>3</sub>). The principal role for these two hormones is to regulate tissue metabolism and, in infants and young children, to regulate growth, development, and maturation of the nervous system and bone and joints. The

enzymatic pathway for the generation of  $T_4$  and  $T_3$  as well as the conversion of  $T_4$  to  $T_3$  (within the liver and the kidneys) are known and genes involved in these pathways are listed in Table 5.

The regulation of thyroid hormone secretion is part of the hypothalamus-pituitary axis; by which thyroid releasing hormone (TRH, secreted from the hypothalamus) acts on the pituitary gland to secrete thyroid-stimulating hormone (TSH) that acts on the thyroid gland to stimulate the secretion of  $T_4$  and  $T_3$ . Somatostatin, and other neuropeptides or neurotransmitters regulate the thyroid gland secretion activity by inhibiting secretion of TSH at the level of the pituitary gland.  $T_3$  can directly suppress the the level of proTRH mRNA in the paraventricular nucleus of the hypothalamus.

Circulating thyroid hormones are bound to throxine-binding globulin, transthyretin, or albumin, which are involved in the transport of the thyroid hormones to their target tissues. The concentrations of these binding proteins change under various physiologic conditions and can affect the efficacy and tissue distribution of the thyroid hormones. These condiditions include 1) increased serum thyroid hormone binding proteins: pregnancy, exposure to supraphysiologic levels of estrogen, hepatic cirrhosis or acute hepatitis, acute intermittent porphyria, exposure to heroin or methadone, and clofibrate; 2) decreased serum thyroid hormone binding proteins: protein malnutrition, hepatic failure, chronic illness, nephrotic syndromes, exposure to L-asparaginase, congenital abnormality (X-linked) of the binding protein genes, exposure to androgenic steroids of pharmacologic doses of glucocorticoids.

The mechanism of action of  $T_3$  and  $T_4$  on the target tissues is thought to occur via thyroid hormone intracellular receptors that binds the hormone ligand and via a process of entry into the nuclear compartment, the hormone-receptor complex activates DNA transcription genes having a thyroid receptor response element in the promoter region.

Dysfunction of thyroid hormone pathway is clinically expressed as either hyperthyroidism or hypothyroidism. In either case, there are multiple levels of possible or potential disruptions of the thyroid hormone signalling pathway.

Hyperthyroidism or Graves' disease is also termed thyroidtoxicosis and may be associated with catecholamine excess, toxic multinodular goiter, toxic adenoma, iodide-induced hyperthyroidism, subacute thyroiditis, factitious (exogenous) thyrotoxicosis, neonatal thyrotoxicosis (mother with Graves' disease), TSH-secreting pituitary tumors, nontumorigenic pituitary-induced hyperthyroidism, choriocarcinoma or hydatiform mole, struma ovarii, and hyperfunctioning thyroid carcinoma. Clinically, symptoms include marked ophthalmopathy (preorbital



swelling, exophthalmos, limitation of extraocular movements, protruding eyes and easy tearing), pretibial myxedema, tachycardia, elevated systolic blood pressure, and increased inotropic activity in the myocardium.

Therapy of hyperthyroidism follows two stages, 1) reestablishment of the euthyroidism, and 2) induction of a permanent alteration of thyroid function. In the first, reduction of elevated thyroid hormone secretion can be achieved by administration of thiourea derivatives (for example, propylthiouracil, methimazole, carbimazole). These agents inhibit the organification of iodine within the thyroid gland and suppress the production of the thyroid hormones. Side effects of these thiourea compounds include maculopapular rash, hepatocellular damage, agranulocytosis, and vasculitis. Other compounds used for the acute therapy of hyperthyroidism include lithium, iopanoic acid, and iopodate. In the second stage of therapy for hyperthyroidism, long-term therapy of propylthiouracil may induce remission of the hypersecretion. If remission is not attained, surgical removal of the thyroid gland, or treatment with  $^{131}\text{I}$ . Unfortunately, radical therapies to remove or ablate function of the thyroid gland can lead to hypothyroidism.

In hypothyroidism, there is impaired secretion of the thyroid hormones. Hypothyroidism may be associated with acquired disease (Hashimoto's thyroiditis, idiopathic myxedema,  $^{131}\text{I}$  radiotherapy, external radiation therapy to the neck area, subacute thyroiditis, cystinosis, impaired function of thyroid gland (iodine deficiency or excess, drug induced (lithium carbonate, para-aminosalicylic acid, thiourea drugs, sulfonamides, phenylbutazone, and others)), congenital genetic defects (biosynthetic enzymes for the thyroid hormones, thyroid agenesis, thyroid dysgenesis or ectopy, maternal iodide or antithyroid drugs), hypothalamic dysfunctions (neoplasms, eosinophilic granuloma, therapeutic irradiation), or pituitary dysfunction (neoplasms, pituitary surgery or irradiation, idiopathic hypopituitarism, Sheehan's syndrome, exposure to supraphysiologic levels of dopamine). Clinically, symptoms include weakness, fatigue, lethargy; dry, coarse skin; swelling of the hands, face and extremities; cold intolerance and decreased sweating; modest weight gain; decreased memory; hearing impairment; arthralgia and paresthesias; constipation; and muscle cramps. In infants or young children in which hypothyroidism remains unchecked during the first two years of life, irreversible mental retardation as part of a syndrome called cretinism develops.

Therapy of hypothyroidism includes the replacement of synthetic thyroid hormones,  $\text{T}_4$  and  $\text{T}_3$ . In these cases, hormone replacement therapy is sufficient to restore euthyroidism. Special cases of hypothyroidism, for example those individuals with angina and hypothyroidism require special monitoring since the replacement hormones may stimulate the myocardial oxygen demands in a

myocardium that can not produce adequate myocardial blood flow. Another special case are patients with severe myxedema coma, and event that may arise in patients with severe hypothyroidism and are subjected to additional physiologic stresses.

Anthithyroid antibodies can be part of an autoimmune thyroid disease, such as Hashimoto's or Graves' disease. Patients may have serum antibodies formed to thyroid peroxidase (common), serum thyroglobulin, or to the TSH receptor.

#### *L. Parathyroid dysfunction*

Parathyroid hormone is secreted by the parathyroid glands. The hormone is responsible for the regulation of bone resorption and calcium mobilization. In addition to increasing the the plasma  $\text{Ca}^{+}$  levels and depressing the plasma phosphate levels, parathyroid hormone increases the excretion of phosphate in the urine.

In cases of pseudohypoparathyroidism, patients have normal circulating levels of parathyroid hormone, but lack the GTP-binding protein to allow hormone receptor-G-protein stimulated adenylate cyclase activity and subsequent increases in intracellular cAMP. In another form of pseudohypoparathyroidism, there is an adequate GTP-binding protein, but there is lacking the intracellular messenger system to allow parathyroid hormone mediated phosphaturic action of the hormone within the target tissues. In cases of parathyroidectomy, hypocalcemia, tetnus, and hyperphosphatemia occurs. Administration of parathyroid hormone can restore calcium and phosphate ion stasis.

In cases of parathyroid hormone excess, usually a result of inordinate administration of parathyroid hormone or a tumor hypersecretion of parathyroid hormone, the symptoms include hypercalcemia, hypophosphatemia, and demineralization of the bones, and the formation of calcium containing kidney stones. Removal of the tumor or adjustment of the parathyroid hormone administration schedule is the prudent course of treatment. Secondary hyperparathyroidism may be the result of chronic renal disease.

In nearly 20% of cancer patients there is marked hypercalcemia as result of bone metastases that produce the hypercalcemia as a result of the eroding bone. The bone erosion may be the result of prostaglandin E and the tumor or cancerous cells. Further some cancers cells hypersecrete 1,25-dihydroxycholecalciferol, or another bone related hormones. In some cancers, there has been detected hypersecretion of parathyroid hormone-related protein. Tumors in this category include breast, kidney, ovary, and skin.

Although the above description includes the hypothalamus-pituitary-target gland axes, there are other organs that have endocrine functions. These include the kidneys, the heart, and the pineal gland.

The kidneys regulate blood pressure via the renin-angiotensin system. The kidneys produce and secrete renin (in the juxtaglomerular apparatus), an acid protease that acts on angiotensinogen to form angiotensin I. The next enzyme in the pathway is angiotensin converting enzyme (ACE, located in the lungs and  
5 elsewhere) which converts angiotensin I to angiotensin II. Angiotensin II acts directly on vascular smooth muscle to to arteriolar constriction and leads to an increase in blood pressure, on the adrenal cortex to stimulate secretion of aldosterone, and in the cerebral cortex to decrease the baroreflex potentiation of the pressor effects. Angiotensin II is metabolized by various peptidases  
10 (aminopeptidase) and is sequestered in vascular beds of tissues by as yet unknown molecule trapping mechanism.

ACE, angiotensin and renin receptors, and regulation of renin secretion have proven excellent candidate targets for drug intervention for the treatment of hypertension and other cardiovascular disease. Other likely candidates for the  
15 therapeutic intervention of the renin-angiotensin system are listed in Table 5 and Table 11.

The kidneys, and to a lesser extent the liver, also produce and secrete erythropoietin. In adults, erythropoietin is produced by the interstitial cells in the peritubular capillary bed of the kidneys and the perivenous hepatocytes in the liver.  
20 Erythropoietin regulates the production of erythrocytes by stimulating the number of erythropoietin-sensitive committed stem cells in the bone marrow that are converted to precursors and ultimately to mature erythrocytes. When erythropoietin levels are low, erythroid stem cells show DNA cleavage followed by programmed cell death (apoptosis). Erythropoietin reduces the DNA cleavage and stimulates the  
25 cells to survive. When the renal mass is reduced in adults by renal disease or nephrectomy, the resultant reduction in the production of erythropoietin, and the inability of the liver production to compensate for this reduction, leads to marked anemia. Synthetic or recombinant erythropoietin has proven to be therapeutically important to those individuals in end-stage renal disease and other anemic conditions  
30 such as cancer, trauma, surgery, and others. Other genes involved in the erythropoietin pathway are listed in Table 5.

The myocardium produces and secretes atrial natriuretic peptide (ANP). ANP produces natriuresis, in part by stimulating an increase in glomerular filtration rate, promotes tubule secretion of sodium, and lowers blood pressure by acting  
35 directly on the vascular smooth muscle cells and decreasing the responsiveness to pressor substances. In the brain, ANP actions are opposite of those directed by angiotensin II. ANP is metabolized by neutral endopeptidase (inhibited by thiorphan) and has a short half-life.

The other endocrine hormone involved in natruiresis is produced and secreted from the adrenal glands and is termed the Na<sup>+</sup>/K<sup>+</sup> ATPase inhibiting factor. This factor produces natruireses by inhibiting the Na<sup>+</sup>/K<sup>+</sup> ATPase and produces an increase in bloo pressure.

5           The pineal gland produces and secretes melatonin. In humans, melatonin is produced and secreted during the dark periods of the day and is maintained at lower concentrations during the daylight hours. Melatonin has been implicated in inducing and maintaining sleep. Melatonin is synthesized from serotonin via two enzymes found in the pineal paremchymal cells. Melatonin is secreted via a neural  
10 stimulation to the pineal gland.  $\beta$ -Adrenergic stimulation to the pineal gland results in increased stimulation of the porduction and screretino of melatonin. Metabolism of melatonin occurs via 6-hydorxylation followed by conjugation in the liver and is predominantly excreted in the urine.

#### Cardiovascular and Renal Disease

15           There are some examples whereby there is no direct evidence that a gene or genes are involved in drug response of a candidate therapeutic intervention. In these cases, however, there is genetic data supporting a role of a variance or variances involved in the etiology, progression, or risk of a cardiovascular or renal disease. These cases, including but excluded to are described below with details of current  
20 therapies and potential genetic involvment of variances in drug responses.

##### *A. Anemia*

          Anemia is a condition in which the number of red blood cells per cubic mm, the amount of hemoglobin in 100 ml of blood, and the volume of packed red cells  
25 per 100 ml of blood are less than normal values. Anemia may be clinically manifested as pallor of the skin and mucus membranes, shortness of breath, palpitations of the heart, soft systolic murmurs, shortness of breath, lethargy, and fatigability or other signs and symptoms. Anemia can be caused by three broad defects 1) bone marrow failure, 2) acute blood loss, and 3) hemolysis, however,  
30 anemia may be the result of one or more of these three. Anemia is a common manifestation of many different chronic or acute diseases, toxins, therapeutic drugs, nutritional status, endocrine disorders, congenital conditions, autoimmune conditions, alcohol, drug, or substance abuse, trauma, surgery, or any other condition that affects the function or status of the bone marrow, blood volume, or  
35 erythrocytes. When anemia develops, there are compensatory physiological mechanisms that are available to attempt to restore tissue oxygenation including

increases in the erythrocyte glycolytic intermediate 2,3-diphosphoglycerate (2,3-DPG; binds to hemoglobin and decreases the oxygen binding affinity) in erythrocytes, increased peripheral dilation, increased cardiac stroke volume, decrease in blood pressure, or other mechanisms.

5           Anemia may be due to drug toxicities. Aplastic anemia or hematologic blood disorders may also be due to a proliferative defect and related bone marrow failure syndromes.

          Anemia due to bone marrow failure usually results in changes in mean cell volume (MCV) can be categorized as normocytic, microcytic, and macrocytic  
10       anemia. Normocytic bone marrow failure can be the result of iron deficiency, chronic disease, renal failure, liver disease, endocrine disorders, aplasia, myelodysplasias, myelofibrosis, hematologic or solid tumors, granulomas, human immunodeficiency virus (HIV) infection, and others. Microcytic bone marrow failure can be the result of iron deficiency, chronic disease, thalassemias, aluminum  
15       toxicity, thyrotoxicosis, hereditary sideroblastic conditions and others. Macrocytic bone marrow failure can be the result of megaloblastic conditions (cobalamin and folate deficiencies, and congenital disorders), alcoholism, drugs, liver disease, aplasia, myelodysplasias, myelofibrosis, hematologica or solid tumors, granulomas, human immunodeficiency virus (HIV) infection, hypothyroidism, splenectomy, and  
20       others.

          Hemolytic anemia primarily due to the destruction of red cells can be the result of congenital conditions (enzyme deficiency, membrane skeletal protein abnormalities, hemoglobinopathies) or acquired conditions (antibody-induced, mechanical fragmentation, and membrane protein anchoring abnormalities). Acute  
25       blood loss occurring in trauma, surgery, or acute or chronic disease can lead to excessive blood loss.

          Drugs or other agents known to cause anemia include cancer chemotherapeutic agents (antimetabolites, alkylating agents, hydroxyurea, cytosine arabinoside and others), anti-inflammatory agents (aspirin, non-steroid anti-  
30       inflammatory agents, phenylbutazone, gold compounds), antibiotics (chloramphenicol, penicillin, cephalosporins, sulfonamides and others), anticonvulsants (phenytoin and others), dihydrofolate reductase inhibitors (methotrexate, pyrimethamine, trimethoprim, triamterene, pentamidene, and others), antiviral agents (zidovudine and others), immunosuppressive agents (azathioprim  
35       and others), antiarrhythmic agents (procainamide, quinidine and others), antihypertensive agents (alpha-methyldopa), antimalarials (primaquine and others), and the anticoagulants (warfarin and heparin and others).

Therapy of anemia includes blood transfusion, removal of the agent or toxin causing the anemia, or treating the underlying cause of the anemia. In some cases of anemia, erythropoietin can be used to stimulate the erythrocyte precursor cells in the bone marrow cells to produce mature erythrocytes.

5 A gene, genes, or gene pathway involved in the etiology of anemia or associated disorders or potential sites for targeted drug therapy of anemia are depicted in Table 11 with the specific gene list in Table 6. Current candidate therapeutic interventions in development for the treatment of anemia are listed in Table 57.

### 10 *B. Angina*

Angina pectoris is a common clinical manifestation of coronary artery disease. Angina is a clinical syndrome including chest pain or discomfort brought on by exertional or anxiety, typically lasting several minutes. Patients with angina are at increased risk of myocardial infarction heart failure and death. Angina is a symptom of myocardial ischemia that is the result of myocardial oxygen demand not met by myocardial oxygen supply (for more details see below under *Ischemia*). Although the most common cause of myocardial ischemia is atherosclerotic coronary artery disease, there are other factors that may lead to this clinical syndrome, including thromboembolic disease and vasospasm. Factors related to myocardial oxygen demand include heart rate, contractility, and wall tension (ventricular volume and ventricular pressure). Unstable angina refers to angina of which occurs at rest or without a specific (exertional or environmental) trigger. Stable angina refers to predictable, event-induced chest pain. Unstable angina has been correlated with progression to acute myocardial infarction in 20% of the cases. More than 50% of the patients with unstable angina have multi-vessel disease with eccentric, irregular, or ulcerated atherosclerotic lesions associated with endothelial disruption and adherent thrombus.

Another form of angina is variant angina which is characterized by chest pain accompanied by a transient ST-segment changes (either ST elevation or depression) and ventricular arrhythmias.

Angina can often be controlled by nitrates,  $\beta$ -adrenergic blockers, calcium channel blockers, antiplatelet and antithrombin therapy, or combination thereof.

35 Genes, and gene pathway involved in the etiology of angina and associated disorders or potential sites for targeted drug therapy of angina are depicted in Table 11 with the specific gene list in Table 6. Current candidate therapeutic interventions in development for the treatment of anemia are listed in Table 58.

### C. Arrhythmia

Cardiac arrhythmias occur as a result of abnormalities of impulse generation, impulse conduction, and combined abnormalities of impulse generation and conduction. Some cardiac arrhythmias may lead to asymptomatic conditions, others lead to clinical symptoms and may be life-threatening. Abnormalities of impulse generation includes abnormal automaticity (abnormal pacemakers), triggered activity as a result of early or delayed after-depolarizations. In both alterations of automaticity and triggered activity, generation of impulses in fibers that are normally incapable of normal automaticity, e.g. atrial and ventricular tissue, ensues. Within the myocardium the conduction system can become a cardiac pacemaker. For example, the atrioventricular (AV) node.

Abnormalities of impulse conduction occurs via a process called reentry. In reentry, there occurs an area or region that is slow or unable to conduct electrical signals. This defect in conduction permits a wave of excitation to propagate continuously within a closed circuit. In these cases, the surrounding tissue is not at the same pace as the surrounding tissue and the electrical impulse passes through the normal tissue and can spread in a multi-directional manner which leads to marked asynchrony.

Heart block is the condition whereby the conduction from the atria to the ventricles is interrupted. Myocardial disease may decrease or stop conduction in one or more regions. Heart block may be complete, incomplete, include a right- or left bundle branch block, hemiblock or fascicular blocks.

Ectopic foci of excitation occurs when there is myocardial disease that renders the His-Purkinje fibers or other fibers to discharge electrical activity spontaneously. This condition leads to increased automaticity, potentially leading to extrasystole, premature beats, atrial or ventricular or nodal paroxysmal tachycardia, or atrial flutter.

Arrhythmias may also be localized to the atrial or ventricular regions. Atrial arrhythmias include atrial tachycardia, or paroxysmal atrial tachycardia with block, atrial flutter, or atrial fibrillation. Ventricular arrhythmias can include all of the previous described types of arrhythmias but also include paroxysmal ventricular tachyarrhythmia as well and ventricular fibrillation.

Accelerated AV conduction (Wolff-Parkinson-White syndrome) or the Lown-Ganong-Levine syndrome are examples of other arrhythmias that are characterized by specific electrocardiogram abnormalities.

Therapy for arrhythmias includes an understanding of the type, underlying mechanism, and treatment targeted to restore normal cardiac function. However, in some cases, mechanisms can only be inferred and therapy is based on empirical

knowledge. Current antiarrhythmic drugs can be classified as the following broad categories: Na<sup>+</sup> channel blockers, K<sup>+</sup> channel blockers, Ca<sup>+</sup> channel blockers,  $\beta$ -adrenergic blockers, and digitalis. In each of these categories, there is a blockade of the activity of the specific ion channel or receptor mediated activation of the myocardial activity. Digitalis is the exception, having multiple pharmacologic effects including Ca<sup>+</sup> current inhibition, stimulation of vagal tone to the myocardium, and a reduction in the K<sup>+</sup> currents within the atrium.

A gene, genes, or gene pathway involved in the etiology of arrhythmia or associated disorders or potential sites for targeted drug therapy of arrhythmia are depicted in Table 11 with the specific gene list in Table 6. Current candidate therapeutic interventions in development for the treatment of arrhythmias are listed in Table 59.

### *Hypertension*

Hypertension is the clinical syndrome in which there is sustained elevation of systemic arterial pressure. There may be conditions of specific arterial hypertension to specific organs, including pulmonary, renal, hepatic arterial hypertension.

Systemic hypertension is a common abnormality that can be the result of a variety of conditions including: adrenocortical disease (Conn's syndrome, aldosteronism, hypersecretion of glucocorticoids, hypersecretion of mineralocorticoids, and pseudohyperaldosteronism), pheochromocytoma, paraganglioma, justaglomerular carcinoma, renal hypertension, renal disease (glomerulonephritis, pyelonephritis, polycystic disease, Liddle's syndrome, hypokalemic nephropathy, low-renin hypotension), Narrowing of the aorta, oral contraceptives, neurovascular compression of the rostral ventrolateral medulla. However, in most cases, the etiology is unknown (termed essential hypertension).

Therapy of hypertension includes  $\alpha$ - or  $\beta$ -adrenergic blockers, inhibition of the renin-angiotension system, or converting enzyme, and calcium channel blockers. In cases whereby hypertension is the result of a condition, as listed above, the primary condition is treated with ancillary antihypertensive added. Further, reduction in the intake of sodium in the diet has been shown to assist the reduction of systemic arterial pressure.

A gene, genes, or gene pathway involved in the etiology of hypertension or associated disorders or potential sites for targeted drug therapy of hypertension are depicted in Table 11 with the specific gene list in Table 6. Current candidate therapeutic interventions in development for the treatment of hypertension are listed in Table 60.



*E. Hypotension*

Hypotension is the condition of subnormal blood pressure. Hypotension may be the result of orthostatic hypotension, anemic conditions, fulminant meningococccemia or other infections, blood transfusions, trauma, traumatic brain injury, hepatic or renal failure, and drug induced.

Hypotension is currently treated with methoamine, peripheral sympathomimetics, and vasopressin. A gene, genes, or gene pathway involved in the etiology of hypotension or associated disorders or potential sites for targeted drug therapy of hypotension are depicted in Table 11 with the specific gene list in Table 6. Current candidate therapeutic interventions in development for the treatment of hypotension are listed in Table 61.

*F. Ischemia*

Myocardial ischemia develops when the metabolic demands exceed oxygen delivery to the myocardium. Factors that influence the myocardial oxygen supply include the oxygen capacity of the blood, coronary blood flow and vascular resistance. Factors that affect myocardial oxygen demand are heart rate, contractility, and systolic wall tension. Any agent or physiologic factor that decreases myocardial oxygen supply or increases myocardial oxygen demand may potentially lead to myocardial ischemia. There are conditions that lead to myocardial ischemia including hypertension, arrhythmias, coronary artery disease, rheumatic fever, congenital heart defects, heart failure, and myocardial infarction.

The identification and extent of myocardial damage due to myocardial oxygen demand and reduced supply clinically manifests as myocardial infarction, sudden death, angina pectoris (either uncomplicated or with infarct), and coronary insufficiency.

Therapies for myocardial ischemia currently available are described within other sections of this invention and can be found under the following sections: thrombosis, angina, hypertension, arrhythmias, and heart failure. A gene, genes, or gene pathway involved in the etiology of ischemia or associated disorders or potential sites for targeted drug therapy of ischemia are depicted in Table 11 with the specific gene list in Table 6. Current candidate therapeutic interventions in development for the treatment of myocardial ischemia are listed in Tables 57, 59, 60, 62, and 64.

*G. Heart Failure*

Heart failure is a syndrome in ventricular dysfunction if accompanied by reduced exercise capacity. Heart failure is the final condition from a variety of cardiovascular disorders including coronary heart disease, long-standing

hypertension, valve deformities or valvular heart disease, rheumatic heart disease, nutritional cardiac disease and cardiomyopathies. Other diseases or conditions associated with heart failure include infections (systemic or cardiac specific (myocarditis), infiltrative disorders (amyloidosis, hemochromatosis, sarcoidosis), electrolyte disorders, myocardial specific toxins (substances of abuse, cancer chemotherapeutic agents), lupus erythmatosus, rheumatoid arthritis, diabetes mellitus, thyroid disease, hypoparathyroidism, pheochromocytoma, and sustained or prolonged tachycardia.

Ultimately, in the failing heart, inotropic action is compromised and the resultant loss in cardiac output renders the myocardium unable to meet the systemic and peripheral metabolic demands leading to various clinical symptoms including cardiac enlargement, weakness, edema, prolonged circulation time, hepatic enlargement, shortness of breath, sensation of suffocation, and distention of peripheral veins. Dyspnea on exertion is a prominent symptom, leading to paroxysmal, and in severe cases, frank pulmonary edema.

Physiological compensatory mechanisms of heart failure can be broadly described as increased heart rate, increased preload and afterload, and cardiac hypertrophy. Each of these physiological changes are attempts to increase cardiac output which is dependent on heart rate, blood pressure and contractility.

Although the most common form of heart failure is left ventricular failure (70-90%), there are conditions whereby diastolic dysfunction occurs (10-30%). Clinically these two are treated differently. For left ventricular (LV) failure, the current therapies include a combination of antihypertensives (ACE inhibitors), diuretics, and positive inotropic agents. Refractory cases of LV failure, additional diuretics, vasodilators, and  $\beta$ -adrenergic blockers are added to the regimen. In diastolic dysfunction leading to failure  $\text{Ca}^{++}$  channel blockers are the first line of therapy with ACE inhibitors and  $\beta$ -adrenergic blockers added in refractory cases.

Heart failure is further associated with a variety of co-morbidities that can worsen the condition and prognosis including septicemia, hypo-osmolality, primary thrombocytopenia, renal hypertension disorder, myocardial infarction, pulmonary embolism, arrhythmias, intracerebral or subdural hemorrhage, cerebral thrombosis, hypotension, pneumonia, chronic renal failure, and decubitus ulcers.

A gene, genes, or gene pathway involved in the etiology of heart failure or associated disorders or potential sites for targeted drug therapy of heart failure are depicted in Table 11 with the specific gene list in Table 6. Current candidate therapeutic interventions in development for the treatment of heart failure are listed

in Table 11 and complications associated with heart failure in Tables 59, 60, 62, and 64.

#### *H. Thrombosis*

5 Thrombosis is the formation of a blood clot in a blood vessel. If the thrombotic clot is large enough it may occlude the vessel and create tissue hypoxia. If unchecked, thrombosis can be a major medical problem and is associated with vessels that have sluggish blood flow, including in veins of extremities after surgery or delivery, conditions of reduced cardiac output, or in coronary or cerebral arteries  
10 where the intima is damaged by atherosclerotic plaques (see below) or damage to the endocardium. Areas of thrombi have a tendency to break off from a vessel wall and can travel to distant sites, termed emboli, and create damage to other organs.

The activation of coagulation occurs via a coordinated process of clotting factors leading to the formation of thrombin which then activates the conversion of  
15 fibrinogen to fibrin and clot formation ensues. However, in the endothelial cell, when thrombin binds to thrombomodulin, thrombin has anticoagulant activity by first activating protein C. Activated protein C then inactivates an inhibitor of tissue plasminogen activator and conversion of plasminogen to plasmin occurs. Plasminogen is converted to active plasmin when tissue plasminogen activator  
20 hydrolyzes the bond between arg560 and val561. Plasmin is responsible for the enzymatic breakdown of clots.

Atherosclerosis is a complex combination of hyperlipidemia, injury to the endothelium, and inflammation. The interaction of these multiple processes in association with local genetic and hemodynamic influences may promote the  
25 formation of atheromatous plaques as a reparative response of the arterial wall. Atherosclerotic plaques are composed of thrombogenic lipid-rich core protected by a fibrous cap comprising smooth muscle cells and inflammatory cells. The inflammatory cells are predominantly macrophages. As atherosclerotic plaques build blood flow is reduced creating ischemia in tissues down stream from the area  
30 of the plaque.

In another model, the stenosis created by the plaques may be a part of the resulting ischemic event. Frequently, less obstructive but more vulnerable plaques occur which are characterized by a thinned fibrous cap, marked lipid accumulation, a large number of macrophages, and a smaller amount of smooth muscle cells. It  
35 has been proposed that since these plaques are more prone to rupture creating contact with the highly thrombogenic materials of the lipid-rich nucleus of these lesions, thrombosis is stimulated.

Advanced atherosclerotic lesions are caused by a series of cellular and molecular events involving replication of smooth muscle cells and macrophages on the vessel wall. The interaction of these cells with the T lymphocytes can lead to a fibroproliferative response. Large amounts of connective tissue produced by these smooth muscle cells consist of macrophages, T lymphocytes, smooth muscle cells, connective tissue, necrotic residues, and varying amounts of lipids and lipoproteins.

Endothelial cells maintain the vessel surface in a non-thrombogenic state, preventing platelet and leukocyte adhesion, and act in maintaining the vascular tonus by releasing nitric oxide, prostaglandin, and endothelin. These cells also produce growth factors, cytokines, and chemokines to maintain the integrity of the collagen- and proteoglycan-rich basement membrane. Changes in some of these functions may trigger cell interactions with monocytes, platelets, smooth muscle cells, and lymphocytes. Hyperlipidemia and hypercholesterolemia are sufficient to induce dysfunction of the endothelial modulation of the vasoactive reactions and arteriolar tonus.

Anticlotting therapy includes heparin, streptokinase, urokinase-type plasminogen activator, and tissue-plasminogen activator. Coumarin derivatives such as dicumarol and warfarin can also be effective anticoagulants. These compounds inhibit the action of vitamin K which is a necessary cofactor for the enzyme that converts glutamic acid residues to  $\gamma$ -carboxyglutamic acid residues. This mechanism affects the clotting factors II, VII, IX, and X, as well as protein C and protein S.

A gene, genes, or gene pathway involved in the etiology of thrombosis or associated disorders or potential sites for targeted drug therapy of thrombosis are depicted in Table 11 with the specific gene list in Table 6. Current candidate therapeutic interventions in development for the treatment of thrombosis are listed in Table 64.

### *I. Renal Disease*

The kidneys are primarily involved in regulating body fluid volume and composition by forming urine. The purpose of urine excretion, composed of ionic solutes, is to remove or eliminate metabolic end-products and maintain fluid volume and composition for the sustenance of physiologic function of the rest of the body. Urine formation and composition is affected by dietary intake of solutes and water as well as endogenous and exogenous carbohydrates, proteins, and nucleic acids. The kidneys also provide the mechanism to excrete drugs, toxins, and other exogenous substances.

Urine formation occurs via a sequence of five steps: 1) the glomerulus filters extracellular fluid across the glomerulus capillaries and the visceral epithelium of Bowman's capsule; the driving force is mean arterial blood pressure; 2) the proximal tubule isototically reabsorbs approximately two-thirds of the glomerular filtrate; 3) the loop of Henle dissociates the absorption of sodium and water; 4) the distal convoluted tubule primarily absorbs sodium under the influence of aldosterone and secretes protons, ammonia, and potassium; and lastly, 5) the collecting duct system regulates the osmolarity of urine under the influence of antidiuretic hormone. In addition to its function of producing urine, the kidney can also serve as an endocrine organ producing and secreting prostaglandins, kallikrein-kinins, erythropoietin, and renin. The kidney also has a function and role in metabolism. The kidney is a target organ for many hormones including parathyroid hormone, aldosterone, and antidiuretic hormone.

Renal dysfunction or disorders often are clinically nonspecific and are characterized by hematuria, azotemia, hypertension, and metabolic acidosis. Broadly, kidney dysfunction can be categorized as underperfusion syndromes, renal parenchymal syndromes, and post-renal syndromes.

Renal underperfusion syndromes include reduced effective circulating volume (including circulatory collapse, congestive heart failure, and cirrhosis of the liver), occlusive renal artery disease (including renal artery atherosclerosis, fibromuscular hyperplasia), and vasoconstriction of renal microvasculature (including acute transplant rejection, cyclosporin nephrotoxicity, and amphotericin B nephrotoxicity).

Renal parenchymal syndromes include acute hypertensive nephropathy, analgesic nephropathy, hemolytic-uremic syndrome, hypercalcemic nephropathy, interstitial nephritis, lupus nephritis, multiple myeloma, oxalate nephropathy, pyelonephritis, glomerulonephritis, renal vein thrombosis, Wegener's granulomatosis.

Renal failure, or the uremic syndrome, occurs when the functional renal mass is sufficiently reduced such that the kidney is longer able to conduct normal functions. Thus, the clinical hallmarks of this disease are related to the loss of urine formation, excretion, and aberrant composition of body fluids as well as loss of erythropoietin and renin and may be treated separately. These related disorders include electrolyte disorders (accumulation of potassium, sodium, phosphate, magnesium and aluminum and hypocalcemia), cardiovascular abnormalities (including accelerated atherosclerosis, hypertension, pericarditis, myocardial dysfunction), hematologic dysfunction (including anemia, leukocyte dysfunction, hemorrhagic diathesis), gastrointestinal disorders (including anorexia, nausea,

vomiting, gastroparesis, gastrointestinal bleeding), disorders of taste, renal osteodystrophy (including osteomalacia, osteitis fibrosa, osteosclerosis, osteoporosis), neurologic abnormalities (including insomnia, fatigue, psychological symptoms, asterixis, peripheral neuropathies), myopathy, impaired carbohydrate intolerance (peripheral resistance to insulin)), endocrine and metabolic disorders (including glucose intolerance, insulin resistance, insulin degradation, hypoglycemia, fertility disorders, hypothermia), hyperuricemia, and pruritis, soft tissue calcification and uremic frost. In chronic renal failure, the loss of renal function may be associated with adaptive functional changes in an attempt to restore renal function. These adaptive processes include increased glomerular filtration rate of the intact nephrons, and increased phosphate excretion. Unfortunately, as the kidney disease and the loss of renal function progresses, these adaptive processes may ultimately create more damage than restore function.

In any of the cases for renal disease there are aggravating factors that can affect the progression of the disease including vascular volume depletion (as a result of diuretics, gastrointestinal fluid losses, dehydration, low cardiac output, renal hypoperfusion, atheroembolic disease, ascites, nephrotic syndrome), drugs (including aminoglycosides, prostaglandin synthesis inhibitors, diuretics), obstructions (including tubule obstruction via uric acid or Bence Jones protein or posttubular obstruction via prostatic hypertrophy, necrotic papillae, or ureteral stones), infections, toxins (including radiographic contrast materials), hypertensive crisis, and hypercalcemia or hyperphosphatemia.

Treatments of renal disease are dependent on whether there is an acute or chronic condition. In the acute conditions, stabilization of fluid and electrolyte balance is critical for the sustenance of life. In chronic end-stage failure the patient may have to depend on exogenous dialysis or transplantation.

A gene, genes, or gene pathway involved in the etiology of renal disease or associated disorders or potential sites for targeted drug therapy of renal disease or associated disorders are depicted in Table 11 with the specific gene list in Table 6. Current candidate therapeutic interventions in development for the treatment of anemia are listed in Table 57, for renal disease in Table 65, and for nephritis in Table 66.

### *J. Restenosis*

Interventional cardiology includes procedures aimed at mechanically improving coronary blood flow. These procedures include intracoronary stents, coronary artery bypass surgery, and percutaneous transluminal coronary angioplasty (PCTA). Although successful resolution of coronary arterial vessel occlusion has

been accomplished with PCTA in as many as two thirds of the patients, currently nearly 20-30% of the patients require emergency bypass surgery, there is an associated 4-10% mortality, 2-5% sustain damage to the vessel including dissection, intimal disruption, perforation, and embolism, and 9% experience Q-wave infarctions. Another PCTA related complication is coronary restenosis. Restenosis, or reocclusion of the coronary vessel, has predisposing factors including male gender, continued smoking after PCTA, diabetes mellitus, elevated insulin levels, absence or previous myocardial infarction, and unstable angina.

A gene, genes, or gene pathway involved in the etiology of restenosis or associated disorders or potential sites for targeted drug therapy of restenosis are depicted in Table 11 with the specific gene list in Table 6. Current candidate therapeutic interventions in development for the treatment of restenosis are listed in Table 67.

#### *K. Peripheral vascular disease*

Peripheral vascular disease (PVD) refers to diseases of any of the blood vessels outside the myocardium and to diseases of the lymph vessels. The disorder is often a narrowing of the blood vessels that carry blood to the arms and legs. There are two types of PVD, functional PVD and organic PVD. Functional PVD is not organic and does not involve defects in the structure of the blood vessels. Functional PVD includes Raynaud's syndrome. Organic PVD are caused by structural changes in the vessel, such as inflammation and tissue damage, for example Buerger's disease. PVD can result from atheromatous narrowing of the arteries to the legs. Symptoms may range from calf pain on exercise "intermittent claudication", to rest pain and gangrene. Intermittent claudication is the commonest symptom occurring in around up to 5% of men and 2.5% of women aged 60 or over. Peripheral vascular disease may be the result of venous stasis, anemia, dysbetalipoproteinemia, diabetes mellitus, and systemic sclerosis.

A gene, genes, or gene pathway involved in the etiology of peripheral vascular disease or associated disorders or potential sites for targeted drug therapy of peripheral vascular disease are depicted in Table 11 with the specific gene list in Table 6. Current candidate therapeutic interventions in development for the treatment of peripheral vascular disease are listed in Table 68.

#### Advantages of Pharmacogenomic Clinical Development of Novel Candidate Therapeutic Interventions for the Treatment of Disease

The evidence that a variance in a gene involved in a pathway that affects drug response, indicates and supports the theory that there is a likelihood that other genes have similar qualities to various degrees. As drug research and development proceeds to identify more lead candidate therapeutic interventions for neurologic and psychiatric disease, there is possible utility in stratifying patients based upon their genotype for these yet to be correlated variances. Further, as described in the Detailed Description, methods for the identification of candidate genes and gene pathways, stratification, clinical trial design, and implementation of genotyping for appropriate medical management of a given disease is easily translated for patients with neurologic and psychiatric disease. As described below there are likely gene pathways as are those that are outlined in the gene pathway Tables 1-6 as described above and matrix Tables 7-11.

The advantages of a clinical research and drug development program that include the use of polymorphic genotyping for the stratification of patients for the appropriate selection of candidate therapeutic intervention includes 1) identification of patients that may respond earlier to therapy, 2) identification of the primary gene and relevant polymorphic variance that directly affects efficacy, safety, or both, 3) identification of pathophysiologic relevant variance or variances and potential therapies affecting those allelic genotypes or haplotypes, and 4) identification of allelic variances or haplotypes in genes that indirectly affects efficacy, safety or both.

Based upon these advantages, designing and performing a clinical trial, either prospective or retrospective, which includes a genotype stratification arm will incorporate analysis of clinical outcomes and potential genetic variation associated with those outcomes, and hypothesis testing of the statistically relevant correlation of the genotypic stratification and therapeutic benefits. If statistical relevance is detectable, these studies will be incorporated into regulatory filings. Ultimately, these clinical trial data will be considered during the approval for marketing process, as well as, incorporated into accepted medical management of the described indications.

By identifying subsets of patients diagnosed with anxiety that respond earlier to agents, optimal candidate therapeutic interventions may reduce the lag time prior to relief of psychiatric symptoms. Appropriate genotyping and correlation to dosing regimen would be beneficial to the patient, caregivers, medical personnel, and the patient's loved ones.

As an example of identification of the primary gene and relevant polymorphic variance that directly affects efficacy, safety, or both one could select a gene pathway as described in the Detailed Description, and determine the effect of



genetic polymorphism and therapy efficacy, safety, or both within that given pathway. By embarking on the previously described gene pathway approach, it is technically feasible to determine the relevant genes within such a targeted drug development program for the clinical indications described in this invention.

5 Identification of pathophysiologic relevant variance or variances and potential therapies affecting those allelic genotypes or haplotypes will speed the drug development. There is a need for therapies that are targeted to the disease and symptom management with limited or no undesirable side effects. Identification of a specific variance or variances within genes involved in the pathophysiologic  
10 manifestation of anxiety and specific genetic polymorphisms of these critical genes can assist the development of novel anxiolytic agents and the identification of those patients that may best benefit from therapy of these candidate therapeutic alternatives.

By identifying allelic variances or haplotypes in genes that indirectly affects  
15 efficacy, safety or both one could target specific secondary drug or agent therapeutic actions that affect the overall therapeutic action of conventional, atypical, or novel action.

In Tables 12-17 and 18-23, there is a listing of candidate genes and specific single nucleotide polymorphisms that may be critical for the identification and  
20 stratification of an anxiety patient population based upon genotype. In matrix Tables 7-11 one skilled in the art would be able to identify these pathway specific genes or other genes listed in Tables 7-11 that may be involved in the manifestation of neurologic or psychiatric disease or are likely candidate targets for therapeutic approaches described in this invention.

25 A sample of therapies approved or in development for preventing or treating the progression of symptoms of cancer currently known in the art are shown in Table 24; for neurologic and psychiatric disease, Tables 25-36; for inflammation and immune disorders, Tables 38-49; for endocrine and metabolic disease, Tables 50-56; and for cardiovascular and renal disease, Tables 57-68. In these tables, the candidate  
30 therapeutics were sorted and listed by mechanism of action. Further, the product name, the pharmacologic mechanism of action, chemical name (if specified), and the indication is listed as well.

Pharmacogenomics studies for these drugs, as well as other agents, drugs,  
35 compounds or candidate therapeutic interventions, could be performed by identifying genes that are involved in the function of a drug including, but not limited to is absorption, distribution metabolism, or elimination, the interaction of the drug with its target as well as potential alternative targets, the response of the cell to the binding of a drug to a target, the metabolism (including synthesis,

biodistribution or elimination) of natural compounds which may alter the activity of the drug by complementary, competitive or allosteric mechanisms that potentiate or limit the effect of the drug, and genes involved in the etiology of the disease that alter its response to a particular class of therapeutic agents. It will be recognized to those skilled in the art that this broadly includes proteins involved in pharmacokinetics as well as genes involved in pharmacodynamics. This also includes genes that encode proteins homologous to the proteins believed to carry out the above functions, which are also worth evaluation as they may carry out similar functions. Together the foregoing proteins constitute the candidate genes for affecting response of a patient to the therapeutic intervention. Using the methods described above, variances in these genes can be identified, and research and clinical studies can be performed to establish an association between a drug response or toxicity and specific variances.

For each of the described disease indications one skilled in the art can identify novel candidate therapeutic interventions that may be used to treat the disease or symptoms and/or proceed with a regimen of palliative care. For compounds that have yet to achieve approval, or are still in development one skilled in the art can determine those candidate therapeutic interventions that may be of therapeutic benefit.

#### Exemplary compounds in development for the treatment of disease disorders or dysfunctions

There are many sources for obtaining information on drugs approved for human therapeutic use and for those compounds under clinical or preclinical investigation, as well as for compounds which have been identified as having a particular pharmacological activity. For products, which have been approved, the PDR contains a listing of the package inserts for all of the products available for human therapeutic intervention. The Merck Index can be used as an additional text to supplement information gathered on the candidate therapeutic interventions. For products that are under clinical or preclinical development, there are databases cataloging information on those candidate therapeutic interventions. Generally that information includes aspects of the drug development process, such as phase of development, identified therapeutic indications, name of manufacturer, mechanistic and pharmacological activities of the product. These databases are available for a fee, and include: PharmaProjects (<http://pjbpubs.co.uk/pharmamain2/html>) and R&D Focus ([http://www.ims.global.com/products/lifecycle/r\\_and\\_d.htm](http://www.ims.global.com/products/lifecycle/r_and_d.htm)). One skilled in the art can readily utilize these sources to determine appropriate candidate therapeutic intervention for the identified disease, disorder or condition.

Since there are a large number of candidate therapeutic interventions that are either approved for human therapeutic use or under clinical or preclinical investigation, one skilled in the art could search through publicly available or fee-for-access databases for interventions that may be of therapeutic benefit for a particular disease, disorder, or condition, and determine whether variances in particular genes correlate with interpatient variation in response to one or more of those therapeutic interventions. An example of the results of such searching is provided in Tables 24-68. In these tables, the disease, disorder or condition is listed. In order to generate a table or other compendium of information as listed in the table, one skilled in the art can search, for example as for Table 35, in databases for products having the indication "schizophrenia". Alternatively, one can search for alternative indications or co-morbidities, e.g., psychoses, neuroleptic, neurological to arrive at a more complete list of the available products. In the table, the candidate therapeutics were sorted and listed by pharmacologic mechanism of action (action). Further, the product name, chemical name (if specified), as well as the indication considered for clinical development. If the candidate therapeutic interventions are approved for therapeutic use, then one skilled in the art can obtain dosing, adverse events, pharmacologic parameters (both pharmacokinetic and pharmacodynamic), and clinical data or information by referring to the PDR. If the candidate therapeutic intervention are in clinical or preclinical stages of drug development, then one skilled in the art would gather data on dosing, adverse events, pharmacologic parameters (both pharmacokinetic and pharmacodynamic), and clinical data or information for the drug or product sponsor. In both cases, selection of a candidate therapeutic intervention for retrospective or prospective pharmacogenetic clinical studies would use an analysis of the likelihood that there is a phenomenological or statistical support for the review of the data to ascertain whether the candidate therapeutic intervention (approved or in development) efficacy or safety profiles can be grouped based upon the individual's genotype or phenotype. In this way, a gene or genes selected, e.g., from a pathway involving the cellular or more broadly the pharmacological mechanism of actions, can be identified and genotyping can be performed in order to determine the allelic variance, variances, for haplotype. Further, one could group the individuals by such genetic variances and further by the therapeutic outcome determinants.

Pharmacogenomics studies for these drugs, as well as other agents, drugs, compounds or candidate therapeutic interventions, can be performed by identifying genes that are involved in the the function of a drug including, but not limited to is absorption, distribution metabolism, or elimination , the interaction of the drug with its target as well as potential alternative targets, the response of the cell to the

binding of a drug to a target, the metabolism (including synthesis, biodistribution or elimination) of natural compounds which may alter the activity of the drug by complementary, competitive or allosteric mechanisms that potentiate or limit the effect of the drug, and genes involved in the etiology of the disease that alter its response to a particular class of therapeutic agents. It will be recognized to those skilled in the art that this broadly includes proteins involved in pharmacokinetics as well as genes involved in pharmacodynamics. This also includes genes that encode proteins homologous to the proteins believed to carry out the above functions, which are also worth evaluation as they may carry out similar functions. Together the foregoing proteins constitute the candidate genes for affecting response of a patient to the therapeutic intervention. Using the methods described above, variances in these genes can be identified, and research and clinical studies can be performed to establish an association between a drug response or toxicity and specific variances.

Further, there may be genes within pathways that are either involved in metabolism of drugs, hormones, compounds, agents, or neurotransmitters or are involved in metabolism of various drugs or compounds. In Tables 1-6 and 12-23, there are listings of candidate genes and specific single nucleotide polymorphisms that may be critical for the identification and stratification of a patient population diagnosed with neurologic or psychiatric disease based upon genotype. Current pathways that may have involvement in the therapeutic benefit of described disease indications of this invention are listed as gene pathways and are listed in Tables 1-23. One skilled in the art would be able to identify these pathway specific gene or genes that may be involved in the manifestation of the described neurological or psychiatric disease, are likely candidate targets for novel therapeutic approaches, or are involved in mediating patient population differences in drug response to therapies for neurological or psychiatric disease described in the present invention.

As indicated in the Summary above, certain aspects of the present invention typically involve the following process, which need not occur separately or in the order stated. Not all of these described processes must be present in a particular method, or need be performed by a single entity or organization or person. Additionally, if certain of the information is available from other sources, that information can be utilized in the present invention. The processes are as follows:

- a) variability between patients in the response to a particular treatment is observed;
- b) at least a portion of the variable response is correlated with the presence or absence of at least one variance in at least one gene;
- c) an analytical or diagnostic test is provided to determine the presence or absence of the at least one variance in individual patients;
- d) the presence or absence of the variance or variances is used

to select a patient for a treatment or to select a treatment for a patient, or the variance information is used in other methods described herein.

#### A. Identification of Interpatient Variability in Response to a Treatment

5 Interpatient variability is the rule, not the exception, in clinical therapeutics. One of the best sources of information on interpatient variability is the nurses and physicians supervising the clinical trial who accumulate a body of first hand observations of physiological responses to the drug in different normal subjects or patients. Evidence of interpatient variation in response can also be measured  
10 statistically, and may be best assessed by descriptive statistical measures that examine variation in response (beneficial or adverse) across a large number of subjects, including in different patient subgroups (men vs. women; whites vs. blacks; Northern Europeans vs. Southern Europeans, etc.).

In accord with the other portions of this description, the present invention concerns  
15 DNA sequence variances that can affect one or more of:

- i. The susceptibility of individuals to a disease;
- ii. The course or natural history of a disease;
- iii. The response of a patient with a disease to a medical intervention, such as, for example, a drug, a biologic substance, physical energy such as radiation therapy, or  
20 a specific dietary regimen. (The terms 'drug', 'compound' or 'treatment' as used herein may refer to any of the foregoing medical interventions.) The ability to predict either beneficial or detrimental responses is medically useful.

Thus variation in any of these three parameters may constitute the basis for initiating a pharmacogenetic study directed to the identification of the genetic  
25 sources of interpatient variation. The effect of a DNA sequence variance or variances on disease susceptibility or natural history (i and ii, above) are of particular interest as the variances can be used to define patient subsets which behave differently in response to medical interventions such as those described in (iii). The methods of this invention are also useful in a clinical development  
30 program where there is not yet evidence of interpatient variation (perhaps because the compound is just entering clinical trials) but such variation in response can be reliably anticipated. It is more economical to design pharmacogenetic studies from the beginning of a clinical development program than to start at a later stage when

the costs of any delay are likely to be high given the resources typically committed to such a program.

In other words, a variance can be useful for customizing medical therapy at least for either of two reasons. First, the variance may be associated with a specific disease subset that behaves differently with respect to one or more therapeutic interventions (i and ii above); second, the variance may affect response to a specific therapeutic intervention (iii above). Consider for exemplary purposes pharmacological therapeutic interventions. In the first case, there may be no effect of a particular gene sequence variance on the observable pharmacological action of a drug, yet the disease subsets defined by the variance or variances differ in their response to the drug because, for example, the drug acts on a pathway that is more relevant to disease pathophysiology in one variance-defined patient subset than in another variance-defined patient subset. The second type of useful gene sequence variance affects the pharmacological action of a drug or other treatment. Effects on pharmacological responses fall generally into two categories; pharmacokinetic and pharmacodynamic effects. These effects have been defined as follows in Goodman and Gilman's Pharmacologic Basis of Therapeutics (ninth edition, McGraw Hill, New York, 1986): "Pharmacokinetics" deals with the absorption, distribution, biotransformations and excretion of drugs. The study of the biochemical and physiological effects of drugs and their mechanisms of action is termed "pharmacodynamics."

Useful gene sequence variances for this invention can be described as variances which partition patients into two or more groups that respond differently to a therapy or that correlate with differences in disease susceptibility or progression, regardless of the reason for the difference, and regardless of whether the reason for the difference is known. The latter is true because it is possible, with genetic methods, to establish reliable associations even in the absence of a pathophysiological hypothesis linking a gene to a phenotype, such as a pharmacological response, disease susceptibility or disease prognosis.

#### B. Identification of Specific Genes and Correlation of Variances in Those Genes with Response to Treatment of Diseases or Conditions

It is useful to identify particular genes which do or are likely to mediate the efficacy or safety of a treatment method for a disease or condition, particularly in view of the large number of genes which have been identified and which continue to be identified in humans. As is further discussed in section C below, this correlation

can proceed by different paths. One exemplary method utilizes prior information on the pharmacology or pharmacokinetics or pharmacodynamics of a treatment method, e.g., the action of a drug, which indicates that a particular gene is, or is likely to be, involved in the action of the treatment method, and further suggests that variances in the gene may contribute to variable response to the treatment method. For example if a compound is known to be glucuronidated then a glucuronyltransferase is likely involved. If the compound is a phenol, the likely glucuronyltransferase is UGT1 (either the UGT1\*1 or UGT1\*6 transcripts, both of which catalyze the conjugation of planar phenols with glucuronic acid). Similar inferences can be made for many other biotransformation reactions.

Alternatively, if such information is not known, variances in a gene can be correlated empirically with treatment response. In this method, variances in a gene which exist in a population can be identified. The presence of the different variances or haplotypes in individuals of a study group, which is preferably representative of a population or populations of known geographic, ethnic and/or racial background, is determined. This variance information is then correlated with treatment response of the various individuals as an indication that genetic variability in the gene is at least partially responsible for differential treatment response. It may be useful to independently analyze variances in the different geographic, ethnic and/or racial groups as the presence of different genetic variances in these groups (i.e. different genetic background) may influence the effect of a specific variance. That is, there may be a gene x gene interaction involving one unstudied gene, however the indicated demographic variables may act as a surrogate for the unstudied allele. Statistical measures known to those skilled in the art are preferably used to measure the fraction of interpatient variation attributable to any one variance, or to measure the response rates in different subgroups defined genetically or defined by some combination of genetic, demographic and clinical criteria.

Useful methods for identifying genes relevant to the pharmacological action of a drug or other treatment are known to those skilled in the art, and include review of the scientific literature combined with inferential or deductive reasoning that one skilled in the art of molecular pharmacology and molecular biology would be capable of; large scale analysis of gene expression in cells treated with the drug compared to control cells; large scale analysis of the protein expression pattern in treated vs. untreated cells, or the use of techniques for identification of interacting proteins or ligand-protein interactions, such as yeast two-hybrid systems.

C. Development of a Diagnostic Test to Determine Variance Status

In accordance with the description in the Summary above, the present invention generally concerns the identification of variances in genes which are indicative of the effectiveness of a treatment in a patient. The identification of specific variances, in effect, can be used as a diagnostic or prognostic test.

Correlation of treatment efficacy and/or toxicity with particular genes and gene families or pathways is provided in Stanton et al., U.S. Provisional Application 60/093,484, filed July 20, 1998, entitled GENE SEQUENCE VARIANCES WITH UTILITY IN DETERMINING THE TREATMENT OF DISEASE (concerns the safety and efficacy of compounds active on folate or pyrimidine metabolism or action) and Stanton, U.S. Provisional Application No. 60/121,047, filed February 22, 1999, entitled GENE SEQUENCE VARIANCES WITH UTILITY IN DETERMINING THE TREATMENT OF DISEASE (concerning Alzheimer's disease and other dementias and cognitive disorders), which are hereby incorporated by reference in their entireties including drawings.

Genes identified in the examples below and in the Tables can be used in the methods of the present invention. A variety of genes which the inventors realize may account for interpatient variation in response to treatments for neurological and psychiatric diseases, conditions, disorders, and/or the development of same are listed in Tables 1-6, and 12-23. Gene sequence variances in said genes are particularly useful for aspects of the present invention.

Methods for diagnostic tests are well known in the art. Generally in this invention, the diagnostic test involves determining whether an individual has a variance or variant form of a gene that is involved in the disease or condition or the action of the drug or other treatment or effects of such treatment. Such a variance or variant form of the gene is preferably one of several different variances or forms of the gene that have been identified within the population and are known to be present at a certain frequency. In an exemplary method, the diagnostic test involves determining the sequence of at least one variance in at least one gene after amplifying a segment of said gene using a DNA amplification method such as the polymerase chain reaction (PCR). In this method DNA for analysis is obtained by amplifying a segment of DNA or RNA (generally after converting the RNA to cDNA) spanning one or more variances in the gene sequence. Preferably, the amplified segment is <500 bases in length, in an alternative embodiment the amplified segment is <100 bases in length, most preferably <45 bases in length.

In some cases it will be desirable to determine a haplotype instead of a genotype. In such a case the diagnostic test is performed by amplifying a segment of DNA or RNA (cDNA) spanning more than one variance in the gene sequence and



preferably maintaining the phase of the variances on each allele. The term "phase" refers to the relationship of variances on a single chromosomal copy of the gene, such as the copy transmitted from the mother (maternal copy or maternal allele) or the father (paternal copy or paternal allele). The haplotyping test may take part in two phases, where first genotyping tests at two or more variant sites reveal which sites are heterozygous in each patient or normal subject. Subsequently the phase of the two or more variant sites can be determined. In performing a haplotyping test preferably the amplified segment is >500 bases in length, more preferably it is >1,000 bases in length, and most preferably it is >2,500 bases in length. One way of preserving phase is to amplify one strand in the PCR reaction. This can be done using one or a pair of oligonucleotide primers that terminate (i.e. have a 3' end that stops) opposite the variant site, such that one primer is perfectly complementary to one variant form and the other primer is perfectly complementary to the other variant form. Other than the difference in the 3' most nucleotide the two primers are identical (forming an allelic primer pair). Only one of the allelic primers is used in any PCR reaction, depending on which strand is being amplified. The primer for the opposite strand may also be an allelic primer, or it may prime from a non-polymorphic region of the template. This method exploits the requirement of most polymerases for perfect complementarity at the 3' terminus of the primer in a primer-template complex. See, for example: Lo YM, Patel P, Newton CR, Markham AF, Fleming KA and JS Wainscoat. (1991) Direct haplotype determination by double ARMS: specificity, sensitivity and genetic applications. *Nucleic Acids Res* July 11;19(13):3561-7.

It is apparent that such diagnostic tests are performed after initial identification of variances within the gene, which allows selection of appropriate allele specific primers.

Diagnostic genetic tests useful for practicing this invention belong to two types: genotyping tests and haplotyping tests. A genotyping test simply provides the status of a variance or variances in a subject or patient. For example suppose nucleotide 150 of hypothetical gene X on an autosomal chromosome is an adenine (A) or a guanine (G) base. The possible genotypes in any individual are AA, AG or GG at nucleotide 150 of gene X.

In a haplotyping test there is at least one additional variance in gene X, say at nucleotide 810, which varies in the population as cytosine (C) or thymine (T). Thus a particular copy of gene X may have any of the following combinations of nucleotides at positions 150 and 810: 150A-810C, 150A-810T, 150G-810C or 150G-810T. Each of the four possibilities is a unique haplotype. If the two nucleotides interact in either RNA or protein, then knowing the haplotype can be

important. The point of a haplotyping test is to determine the haplotypes present in a DNA or cDNA sample (e.g. from a patient). In the example provided there are only four possible haplotypes, but, depending on the number of variances in the gene and their distribution in human populations there may be three, four, five, six or  
5 more haplotypes at a given gene. The most useful haplotypes for this invention are those which occur commonly in the population being treated for a disease or condition. Preferably such haplotypes occur in at least 5% of the population, more preferably in at least 10%, still more preferably in at least 20% of the population and most preferably in at least 30% or more of the population. Conversely, when the  
10 goal of a pharmacogenetic program is to identify a relatively rare population that has an adverse reaction to a treatment, the most useful haplotypes may be rare haplotypes, which may occur in less than 5%, less than 2%, or even in less than 1% of the population. One skilled in the art will recognize that the frequency of the adverse reaction provides a useful guide to the likely frequency of salient causative  
15 haplotypes.

Based on the identification of variances or variant forms of a gene, a diagnostic test utilizing methods known in the art can be used to determine whether a particular form of the gene, containing specific variances or haplotypes, or combinations of variances and haplotypes, is present in at least one copy, one copy,  
20 or more than one copy in an individual. Such tests are commonly performed using DNA or RNA collected from blood, cells, tissue scrapings or other cellular materials, and can be performed by a variety of methods including, but not limited to, PCR based methods, hybridization with allele-specific probes, enzymatic mutation detection, chemical cleavage of mismatches, mass spectrometry or DNA  
25 sequencing, including minisequencing. Methods for haplotyping are described above. In particular embodiments, hybridization with allele specific probes can be conducted in two formats: (1) allele specific oligonucleotides bound to a solid phase (glass, silicon, nylon membranes) and the labelled sample in solution, as in many DNA chip applications, or (2) bound sample (often cloned DNA or PCR amplified  
30 DNA) and labelled oligonucleotides in solution (either allele specific or short – e.g. 7mers or 8mers - so as to allow sequencing by hybridization). Preferred methods for diagnostic testing of variances are described in four patent applications Stanton et al, entitled A METHOD FOR ANALYZING POLYNUCLEOTIDES, serial numbers  
09/394,467; 09/394,457; 09/394,774; and 09/394,387; all filed September 10, 1999.  
35 The application of such diagnostic tests is possible after identification of variances that occur in the population. Diagnostic tests may involve a panel of variances from one or more genes, often on a solid support, which enables the simultaneous determination of more than one variance in one or more genes.

#### D. Use of Variance Status to Determine Treatment

The present disclosure describes exemplary gene sequence variances in genes identified in a gene table herein (e.g., Tables 12-17 and 18-23), and variant forms of these gene that may be determined using diagnostic tests. As indicated in the Summary, such a variance-based diagnostic test can be used to determine whether or not to administer a specific drug or other treatment to a patient for treatment of a disease or condition. Preferably such diagnostic tests are incorporated in texts such as are described in Clinical Diagnosis and Management by Laboratory Methods (19th Ed) by John B. Henry (Editor) W B Saunders Company, 1996; Clinical Laboratory Medicine : Clinical Application of Laboratory Data, (6th edition) by R. Ravel, Mosby-Year Book, 1995, or other medical textbooks including, without limitation, textbooks of medicine, laboratory medicine, therapeutics, pharmacy, pharmacology, nutrition, allopathic, homeopathic, and osteopathic medicine; preferably such a test is developed as a 'home brew' method by a certified diagnostic laboratory; most preferably such a diagnostic test is approved by regulatory authorities, e.g., by the U.S. Food and Drug Administration, and is incorporated in the label or insert for a therapeutic compound, as well as in the Physicians Desk Reference.

In such cases, the procedure for using the drug is restricted or limited on the basis of a diagnostic test for determining the presence of a variance or variant form of a gene. Alternatively the use of a genetic test may be advised as best medical practice, but not absolutely required, or it may be required in a subset of patients, e.g. those using one or more other drugs, or those with impaired liver or kidney function. The procedure that is dictated or recommended based on genotype may include the route of administration of the drug, the dosage form, dosage, schedule of administration or use with other drugs; any or all of these may require selecting or determination consistent with the results of the diagnostic test or a plurality of such tests. Preferably the use of such diagnostic tests to determine the procedure for administration of a drug is incorporated in a text such as those listed above, or medical textbooks, for example, textbooks of medicine, laboratory medicine, therapeutics, pharmacy, pharmacology, nutrition, allopathic, homeopathic, and osteopathic medicine. As previously stated, preferably such a diagnostic test or tests are required by regulatory authorities and are incorporated in the label or insert as well as the Physicians Desk Reference.

Variances and variant forms of genes useful in conjunction with treatment methods may be associated with the origin or the pathogenesis of a disease or condition. In many useful cases, the variant form of the gene is associated with a

specific characteristic of the disease or condition that is the target of a treatment, most preferably response to specific drugs or other treatments. Examples of diseases or conditions ameliorable by the methods of this invention are identified in the Examples and tables below; in general treatment of disease with current methods, particularly drug treatment, always involves some unknown element (involving efficacy or toxicity or both) that can be reduced by appropriate diagnostic methods.

Alternatively, the gene is involved in drug action, and the variant forms of the gene are associated with variability in the action of the drug. For example, in some cases, one variant form of the gene is associated with the action of the drug such that the drug will be effective in an individual who inherits one or two copies of that form of the gene. Alternatively, a variant form of the gene is associated with the action of the drug such that the drug will be toxic or otherwise contra-indicated in an individual who inherits one or two copies of that form of the gene.

In accord with this invention, diagnostic tests for variances and variant forms of genes as described above can be used in clinical trials to demonstrate the safety and efficacy of a drug in a specific population. As a result, in the case of drugs which show variability in patient response correlated with the presence or absence of a variance or variances, it is preferable that such drug is approved for sale or use by regulatory agencies with the recommendation or requirement that a diagnostic test be performed for a specific variance or variant form of a gene which identifies specific populations in which the drug will be safe and/or effective. For example, the drug may be approved for sale or use by regulatory agencies with the specification that a diagnostic test be performed for a specific variance or variant form of a gene which identifies specific populations in which the drug will be toxic. Thus, approved use of the drug, or the procedure for use of the drug, can be limited by a diagnostic test for such variances or variant forms of a gene; or such a diagnostic test may be considered good medical practice, but not absolutely required for use of the drug.

As indicated, diagnostic tests for variances as described in this invention may be used in clinical trials to establish the safety and efficacy of a drug. Methods for such clinical trials are described below and/or are known in the art and are described in standard textbooks. For example, diagnostic tests for a specific variance or variant form of a gene may be incorporated in the clinical trial protocol as inclusion or exclusion criteria for enrollment in the trial, to allocate certain patients to treatment or control groups within the clinical trial or to assign patients to different treatment cohorts. Alternatively, diagnostic tests for specific variances may be performed on all patients within a clinical trial, and statistical analysis performed comparing and contrasting the efficacy or safety of a drug between individuals with

different variances or variant forms of the gene or genes. Preferred embodiments involving clinical trials include the genetic stratification strategies, phases, statistical analyses, sizes, and other parameters as described herein.

Similarly, diagnostic tests for variances can be performed on groups of patients known to have efficacious responses to the drug to identify differences in the frequency of variances between responders and non-responders. Likewise, in other cases, diagnostic tests for variance are performed on groups of patients known to have toxic responses to the drug to identify differences in the frequency of the variance between those having adverse events and those not having adverse events. Such outlier analyses may be particularly useful if a limited number of patient samples are available for analysis. It is apparent that such clinical trials can be or are performed after identifying specific variances or variant forms of the gene in the population. In defining outliers it is useful to examine the distribution of responses in the placebo group; outliers should preferably have responses that exceed in magnitude the extreme responses in the placebo group.

The identification and confirmation of genetic variances is described in certain patents and patent applications. The description therein is useful in the identification of variances in the present invention. For example, a strategy for the development of anticancer agents having a high therapeutic index is described in Housman, International Application PCT/US94/08473 and Housman, INHIBITORS OF ALTERNATIVE ALLELES OF GENES ENCODING PROTEINS VITAL FOR CELL VIABILITY OR CELL GROWTH AS A BASIS FOR CANCER THERAPEUTIC AGENTS, U.S. Patent 5,702,890, issued December 30, 1997, which are hereby incorporated by reference in their entireties. Also, a number of gene targets and associated variances are identified in Housman et al., PCT/US98/05419, entitled TARGET ALLELES FOR ALLELE-SPECIFIC DRUGS, filed March 19, 1998, which is hereby incorporated by reference in its entirety, including drawings.

The described approach and techniques are applicable to a variety of other diseases, conditions, and/or treatments and to genes associated with the etiology and pathogenesis of such other diseases and conditions and the efficacy and safety of such other treatments.

Useful variances for this invention can be described generally as variances which partition patients into two or more groups that respond differently to a therapy (a therapeutic intervention), regardless of the reason for the difference, and regardless of whether the reason for the difference is known.

### III. From Variance List to Clinical Trial: Identifying Genes and Gene Variances that Account for Variable Responses to Treatment

There are a variety of useful methods for identifying a subset of genes from a large set of candidate genes that should be prioritized for further investigation with respect to their influence on inter-individual variation in disease predisposition or response to a particular drug. These methods include for example, (1) searching the biomedical literature to identify genes relevant to a disease or the action of a drug, (2) screening the genes identified in step 1 for variances. A large set of exemplary variances are provided in Tables 12-23. Other methods include (3) using computational tools to predict the functional effects of variances in specific genes, (4) using *in vitro* or *in vivo* experiments to identify genes which may participate in the response to a drug or treatment, and to determine the variances which affect gene, RNA or protein function, and may therefore be important genetic variables affecting disease manifestations or drug response, and (5) retrospective or prospective clinical trials. Computational tools are described in U.S. Patent Application, Stanton et al., serial number, attorney docket number 241/034, filed April 26, 1999, entitled GENE SEQUENCE VARIANCES WITH UTILITY IN DETERMINING THE TREATMENT OF DISEASE, and in Stanton et al., Serial No. 09/419,705, filed October 14, 1999, entitled VARIANCE SCANNING METHOD FOR IDENTIFYING GENE SEQUENCE VARIANCES, which are hereby incorporated by reference in their entireties, including drawings. Other methods are considered below in some detail.

(1) To begin, one preferably identifies, for a given treatment, a set of candidate genes that are likely to affect disease phenotype or drug response. This can be accomplished most efficiently by first assembling the relevant medical, pharmacological and biological data from available sources (e.g., public databases and publications). One skilled in the art can review the literature (textbooks, monographs, journal articles) and online sources (databases) to identify genes most relevant to the action of a specific drug or other treatment, particularly with respect to its utility for treating a specific disease, as this beneficially allows the set of genes to be analyzed ultimately in clinical trials to be reduced from an initial large set. Specific strategies for conducting such searches are described below. In some instances the literature may provide adequate information to select genes to be studied in a clinical trial, but in other cases additional experimental investigations of the sort described below will be preferable to maximize the likelihood that the salient genes and variances are moved forward into clinical studies. Specific genes relevant to understanding

interpatient variation in response to treatments for major neurological and psychiatric diseases are listed in Tables 1-6. In Tables 7-11 preferred sets of genes for analysis of variable therapeutic response in specific diseases are highlighted. These genes are exemplary; they do not constitute a complete set of genes that may account for variation in clinical response. Experimental data are also useful in establishing a list of candidate genes, as described below.

- (2) Having assembled a list of candidate genes generally the second step is to screen for variances in each candidate gene. Experimental and computational methods for variance detection are described in this invention, and tables of exemplary variances are provided (Tables 12-23) as well as methods for identifying additional variances and a written description of such possible additional variances in the cDNAs of genes that may affect drug action (see Stanton et al., Application No. 09/300,747, filed April 26, 1999, entitled GENE SEQUENCE VARIANCES WITH UTILITY IN DETERMINING THE TREATMENT OF DISEASE, incorporated in its entirety.
- (3) Having identified variances in candidate genes the next step is to assess their likely contribution to clinical variation in patient response to therapy, preferably by using informatics-based approaches such as DNA and protein sequence analysis and protein modeling. The literature and informatics-based approaches provide the basis for prioritization of candidate genes, however it may in some cases be desirable to further narrow the list of candidate genes, or to measure experimentally the phenotype associated with specific variances or sets of variances (e.g. haplotypes).
- (4) Thus, as a third step in candidate gene analysis, one skilled in the art may elect to perform *in vitro* or *in vivo* experiments to assess the functional importance of gene variances, using either biochemical or genetic tests. (Certain kinds of experiments – for example gene expression profiling and proteome analysis - may not only allow refinement of a candidate gene list but may also lead to identification of additional candidate genes.) Combination of two or all of the three above methods will provide sufficient information to narrow and prioritize the set of candidate genes and variances to a number that can be studied in a clinical trial with adequate statistical power.
- (5) The fourth step is to design retrospective or prospective human clinical trials to test whether the identified allelic variance, variances, or haplotypes or combination thereof influence the efficacy or toxicity profiles for a given drug or

other therapeutic intervention. It should be recognized that this fourth step is the crucial step in producing the type of data that would justify introducing a diagnostic test for at least one variance into clinical use. Thus while each of the above four steps are useful in particular instances of the invention, this final step is indispensable. Further guidance and examples of how to perform these five steps are provided below.

(6) A fifth (optional) step entails methods for using a genotyping test in the promotion and marketing of a treatment method. It is widely appreciated that there is a tendency in the pharmaceutical industry to develop many compounds for well established therapeutic targets. Examples include beta adrenergic blockers, hydroxymethylglutaryl (HMG) CoA reductase inhibitors (statins), dopamine D2 receptor antagonists and serotonin transporter inhibitors. Frequently the pharmacology of these compounds is quite similar in terms of efficacy and side effects. Therefore the marketing of one compound vs. other members of the class is a challenging problem for drug companies, and is reflected in the lesser success that late products typically achieve compared to the first and second approved products. It occurred to the inventors that genetic stratification can provide the basis for identifying a patient population with a superior response rate or improved safety to one member of a class of drugs, and that this information can be the basis for commercialization of that compound. Such a commercialization campaign can be directed at caregivers, particularly physicians, or at patients and their families, or both.

#### 1. Identification of Candidate Genes Relevant to the Action of a Drug

Practice of this invention will often begin with identification of a specific pharmaceutical product, for example a drug, that would benefit from improved efficacy or reduced toxicity or both, and the recognition that pharmacogenetic investigations as described herein provide a basis for achieving such improved characteristics. The question then becomes which genes and variances, such as those provided in this application in Tables 1-6, 12-17, and 18-23, would be most relevant to interpatient variation in response to the drug. As discussed above, the set of relevant genes includes both genes involved in the disease process and genes involved in the interaction of the patient and the treatment – for example genes involved in pharmacokinetic and pharmacodynamic action of a drug. The biological and biomedical literature and online databases provide useful guidance in selecting such genes. Specific guidance in the use of these resources is provided below.



*Review the literature and online sources*

One way to find genes that affect response to a drug in a particular disease setting is to review the published literature and available online databases regarding the pathophysiology of the disease and the pharmacology of the drug. Literature or  
5 online sources can provide specific genes involved in the disease process or drug response, or describe biochemical pathways involving multiple genes, each of which may affect the disease process or drug response.

Alternatively, biochemical or pathological changes characteristic of the disease may be described; such information can be used by one skilled in the art to  
10 infer a set of genes that can account for the biochemical or pathologic changes. For example, to understand variation in response to a drug that modulates serotonin levels in a central nervous system (CNS) disorder associated with altered levels of serotonin one would preferably study, at a minimum, variances in genes responsible for serotonin biosynthesis, release from the cell, receptor binding, presynaptic  
15 reuptake, and degradation or metabolism. Genes responsible for each of these functions should be examined for variation that may account for interpatient differences in drug response or disease manifestations. As recognized by those skilled in the art, a comprehensive list of such genes can be obtained from textbooks, monographs and the literature.

20 There are several types of scientific information, described in some detail below, that are valuable for identifying a set of candidate genes to be investigated with respect to a specific disease and therapeutic intervention. First there is the medical literature, which provides basic information on disease pathophysiology and therapeutic interventions. A subset of this literature is devoted to specific  
25 description of pathologic conditions. Second there is the pharmacology literature, which will provide additional information on the mechanism of action of a drug (pharmacodynamics) as well as its principal routes of metabolic transformation (pharmacokinetics) and the responsible proteins. Third there is the biomedical literature (principally genetics, physiology, biochemistry and molecular biology),  
30 which provides more detailed information on metabolic pathways, protein structure and function and gene structure. Fourth, there are a variety of online databases that provide additional information on metabolic pathways, gene families, protein function and other subjects relevant to selecting a set of genes that are likely to affect the response to a treatment.

*Medical Literature*

A good starting place for information on molecular pathophysiology of a specific disease is a general medical textbook such as Harrison's Principles of Internal Medicine, 14th edition, (2 Vol Set) by A.S. Fauci, E. Braunwald, K.J. Isselbacher, et al. (editors), McGraw Hill, 1997, or Cecil Textbook of Medicine (20th Ed) by R. L. Cecil, F. Plum and J. C. Bennett (Editors) W B Saunders Co., 1996. For pediatric diseases texts such as Nelson Textbook of Pediatrics (15th edition) by R.E. Behrman, R.M. Kliegman, A.M. Arvin and W.E. Nelson (Editors), W B Saunders Co., 1995 or Oski's Principles and Practice of Pediatrics (3<sup>rd</sup> Edition) by J.A. Mamillan & F.A. Oski Lippincott-Raven, 1999 are useful introductions. For obstetrical and gynecological disorders texts such as Williams Obstetrics (20th Ed) by F.G. Cunningham, N.F. Gant, P.C. McDonald et al. (Editors), Appleton & Lange, 1997 provide general information on disease pathophysiology. For psychiatric disorders texts such as the Comprehensive Textbook of Psychiatry, VI (2 Vols) by H.I. Kaplan and B.J. Sadock (Editors), Lippincott, Williams & Wilkins, 1995, or The American Psychiatric Press Textbook of Psychiatry (3<sup>rd</sup> edition) by R.E. Hales, S.C. Yudofsky and J.A. Talbott (Editors) Amer Psychiatric Press, 1999 provide an overview of disease nosology, pathophysiological mechanisms and treatment regimens.

In addition to these general texts, there are a variety of more specialized medical texts that provide greater detail about specific disorders which can be utilized in developing a list of candidate genes and variances relevant to interpatient variation in response to a treatment. For example, within the field of medicine there are standard textbooks for each of the subspecialties. Some examples include:

Heart Disease: A Textbook of Cardiovascular Medicine (2 Volume set) by E. Braunwald (Editor), W B Saunders Co., 1996; Hurst's the Heart, Arteries and Veins (9th Ed) (2 Vol Set) by R.W. Alexander, R.C. Schlant, V. Fuster, W. Alexander and E.H. Sonnenblick (Editors) McGraw Hill, 1998; Principles of Neurology (6th edition) by R.D. Adams, M. Victor (editors), and A.H. Ropper (Contributor), McGraw Hill, 1996; Sleisenger & Fordtran's Gastrointestinal and Liver Disease: Pathophysiology, Diagnosis, Management (6th edition) by M. Feldman, B.F. Scharschmidt and M. Sleisenger (Editors), W B Saunders Co., 1997; Textbook of Rheumatology (5th edition) by W.N. Kelley, S. Ruddy, E.D. Harris Jr. and C.B. Sledge (Editors) (2 volume set) W B Saunders Co., 1997; Williams Textbook of Endocrinology (9th edition) by J.D. Wilson, D.W. Foster, H. M. Kronenberg and Larsen (Editors), W B Saunders Co., 1998; Wintrobe's Clinical Hematology (10th Ed) by G.R. Lee, J. Foerster (Editor) and J. Lukens (Editors) (2 Volumes) Lippincott, Williams & Wilkins, 1998; Cancer: Principles & Practice of Oncology

(5th edition) by V.T. Devita, S.A. Rosenberg and S. Hellman (editors), Lippincott-Raven Publishers, 1997; Principles of Pulmonary Medicine (3rd edition) by S.E. Weinberger & J Fletcher (Editors), W B Saunders Co., 1998; Diagnosis and Management of Renal Disease and Hypertension (2nd edition) by A.K. Mandal & J.C. Jennette (Editors), Carolina Academic Press, 1994. Massry & Glassock's Textbook of Nephrology (3rd edition) by S.G. Massry & R.J. Glassock (editors) Williams & Wilkins, 1995; The Management of Pain by J.J. Bonica, Lea and Febiger, 1992; Ophthalmology by M. Yanoff & J.S. Duker, Mosby Year Book, 1998; Clinical Ophthalmology: A Systemic Approach by J.J. Kanski, Butterworth-Heinemann, 1994; and Essential Otolaryngology by J.K. Lee Appleton and Lange 1998.

In addition to these subspecialty texts there are many textbooks and monographs that concern more restricted disease areas, or specific diseases. Such books provide more extensive coverage of pathophysiologic mechanisms and therapeutic options. The number of such books is too great to provide examples for all but a few diseases, however one skilled in the art will be able to readily identify relevant texts. One simple way to search for relevant titles is to use the search engine of an online bookseller such as <http://www.amazon.com> or <http://www.barnesandnoble.com> using the disease or drug (or the group of diseases or drugs to which they belong) as search terms. For example a search for asthma would turn up titles such as Asthma : Basic Mechanisms and Clinical Management (3rd edition) by P.J. Barnes, I.W. Rodger and N.C. Thomson (Editors), Academic Press, 1998 and Airways and Vascular Remodelling in Asthma and Cardiovascular Disease : Implications for Therapeutic Intervention, by C. Page & J. Black (Editors), Academic Press, 1994.

### *Pathology Literature*

In addition to medical texts there are texts that specifically address disease etiology and pathologic changes associated with disease. A good general pathology text is Robbins Pathologic Basis of Disease (6th edition) by R.S. Cotran, V. Kumar, T. Collins and S.L. Robbins, W B Saunders Co., 1998. Specialized pathology texts exist for each organ system and for specific diseases, similar to medical texts. These texts are useful sources of information for one skilled in the art for developing lists of genes that may account for some of the known pathologic changes in disease tissue. Exemplary texts are as follows:

Bone Marrow Pathology 2<sup>nd</sup> edition, by B.J. Bain, I. Lampert. & D. Clark, Blackwell Science, 1996; Atlas of Renal Pathology by F.G. Silva, W.B. Saunders,

1999; Fundamentals of Toxicologic Pathology by W.M. Haschek and C.G. Rousseaux, Academic Press, 1997; Gastrointestinal Pathology by P. Chandrasoma, Appleton and Lange, 1998; Ophthalmic Pathology with Clinical Correlations by J. Sassani, Lippincott-Raven, 1997; Pathology of Bone and Joint Disorders by F. McCarthy, F.J. Frassica and A. Ross, W. B. Saunders, 1998; Pulmonary Pathology by M.A. Grippi, Lippincott-Raven, 1995; Neuropathology by D. Ellison, L. Chimelli, B. Harding, S. Love & J. Lowe, Mosby Year Book, 1997; Greenfield's Neuropathology 6<sup>th</sup> edition by J.G. Greenfield, P.L. Lantos & D.I. Graham, Edward Arnold, 1997.

10 *Pharmacology, Pharmacogenetics and Pharmacy Literature*

There are also both general and specialized texts and monographs on pharmacology that provide data on pharmacokinetics and pharmacodynamics of drugs. The discussion of pharmacodynamics (mechanism of action of the drug) in such texts is often supported by a review of the biochemical pathway or pathways that are

15 affected by the drug. Also, proteins related to the target protein are often listed; it is important to account for variation in such proteins as the related proteins may be involved in drug pharmacology. For example, there are 14 known serotonin receptors. Various pharmacological serotonin agonists or antagonists have different affinities for these different receptors. Variation in a specific receptor may affect the

20 pharmacology not only of drugs targeted to that receptor, but also drugs that are principally agonists or antagonists of different receptors. Such compounds may produce different effects on two allelic forms of a non-targeted receptor; for example on variant form may bind the compound with higher affinity than the other, or a compound that is principally an antagonist for one allele may be a partial

25 agonist for another allele. Thus genes encoding proteins structurally related to the target protein should be screened for variance in order to successfully realize the methods of the present invention. A good general pharmacology text is Goodman & Gilman's the Pharmacological Basis of Therapeutics (9th Ed) by J.G. Hardman, L.E. Limbird, P.B. Molinoff, R.W. Ruddon and A.G. Gilman (Editors) McGraw Hill,

30 1996. There are also texts that focus on the pharmacology of drugs for specific disease areas, or specific classes of drugs (e.g. natural products) or adverse drug interactions, among other subjects. Specific examples include:

The American Psychiatric Press Textbook of Psychopharmacology (2nd edition) by A.F. Schatzberg & C.B. Nemeroff (Editors), American Psychiatric Press, 1998; and

35 Essential Psychopharmacology : Neuroscientific Basis and Practical Applications by N. Muntner and S.M. Stahl, Cambridge Univ Press, 1996.

There are also texts on pharmacogenetics which are particularly useful for identifying genes which may contribute to variable pharmacokinetic response. In addition there are texts on some of the major xenobiotic metabolizing proteins, such as the cytochrome P450 genes including Pharmacogenetics of Drug Metabolism (International Encyclopedia of Pharmacology and Therapeutics) by Werner Kalow (Editor) Pergamon Press, 1992; Genetic Factors in Drug Therapy : Clinical and Molecular Pharmacogenetics by D.A Price Evans, Cambridge Univ Press, 1993; Pharmacogenetics (Oxford Monographs on Medical Genetics, 32) by W.W. Weber, Oxford Univ Press, 1997; Cytochrome P450 : Structure, Mechanism, and Biochemistry by P.R. Ortiz de Montellano (Editor), Plenum Publishing Corp, 1995; and Appleton & Lange's Review of Pharmacy, 6<sup>th</sup> edition, (Appleton & Lange's Review Series) by G.D. Hall & B.S. Reiss, Appleton & Lange, 1997.

#### *Genetics, Biochemistry and Molecular Biology Literature*

In addition to the medical, pathology, and pharmacology texts listed above there are several information sources that one skilled in the art will turn to for information on the genetic, physiologic, biochemical, and molecular biological aspects of the disease, disorder or condition or the effect of the therapeutic intervention on specific physiologic processes. The biomedical literature may include information on nonhuman organisms that is relevant to understanding the likely disease or pharmacological pathways in man.

Also provided below are illustrative texts which will aid in the identification of a pathway or pathways, and a gene or genes that may be relevant to interindividual variation in response to a therapy. Textbooks of biochemistry, genetics and physiology are often useful sources for such pathway information. In order to ascertain the appropriate methods to analyze the effects of an allelic variance, variances, or haplotypes in vitro, one skilled in the art will review existing information on molecular biology, cell biology, genetics, biochemistry; and physiology. Such texts are useful sources for general and specific information on the genetic and biochemical processes involved in disease and in drug action, as well as experimental procedures that may be useful in performing in vitro research on an allelic variance, variances, or haplotye.

Texts on gene structure and function and RNA biochemistry will be useful in evaluating the consequences of variances that do not change the coding sequence

(silent variances). Such variances may alter the interaction of RNA with proteins or other regulatory molecules affecting RNA processing, polyadenylation, or export.

*Molecular and Cellular Biology*

Molecular Cell Biology by H. Lodish, D. Baltimore, A. Berk, L. Zipurksy & J.  
5 Darnell, W H Freeman & Co., 1995; Essentials of Molecular Biology, D. Freifelder  
and Malacinski, Jones and Bartlett, 1993; Genes and Genomes: A Changing  
Perspective, M. Singer and P. Berg, University Science Books, 1991; Gene  
Structure and Expression, J.D. Hawkins, 1996. Cambridge University Press;  
Molecular Biology of the Cell, 2nd edition, B. Alberts et al., Garland Publishing,  
10 1994.

*Molecular Genetics*

The Metabolic and Molecular Bases of Inherited Disease by C. R. Scriver, A.L.  
Beaudet, W.S. Sly (Editors), 7th edition, McGraw Hill, 1995; Genetics and  
15 Molecular Biology, R. Schleif, 1994. 2nd edition, Johns Hopkins University Press;  
Genetics, P.J. Russell, 1996. 4th edition, Harper Collins; An Introduction to Genetic  
Analysis, Griffiths et al. 1993. 5th edition, W.H. Freeman and Company;  
Understanding Genetics: A molecular approach, Rothwell, 1993. Wiley-Liss

*General Biochemistry*

Biochemistry, L. Stryer, 1995. W.H. Freeman and Company; Biochemistry, D.  
Voet and J.G. Voet, 1995. John Wiley and Sons; Principles of Biochemistry, A.L.  
Lehninger, D.L. Nelson, and M.M. Cox, 1993. Worth Publishers; Biochemistry, G.  
Zubay, 1998. Wm. C. Brown Communications; Biochemistry, C.K. Mathews and  
25 K.E. van Holde, 1990. Benjamin/Cummings

*Transcription*

Eukaryotic Transcription Factors, D.S. Latchman, 1995. Academic Press;  
Eukaryotic Gene Transcription, S. Goodbourn (ed.), 1996. Oxford University Press;  
30 Transcription Factors and DNA Replication, D.S. Pederson and N.H. Heintz, 1994.  
CRC Press/R.G. Landes Company; Transcriptional Regulation, S.L. McKnight and  
K. Yamamoto (eds.), 1992. 2 volumes, Cold Spring Harbor Laboratory Press

*RNA*

Control of Messenger RNA Stability, J. Belasco and G. Brawerman (eds.), 1993.  
35 Academic Press; RNA-Protein Interactions, Nagai and Mattaj (eds.), 1994. Oxford

University Press; mRNA Metabolism and Post-transcriptional Gene Regulation, Harford and Morris (eds.), 1997. Wiley-Liss.

### *Translation*

- 5 Translational Control, J.W.B. Hershey, M.B. Mathews, and N. Sonenberg (eds.), 1995. Cold Spring Harbor Laboratory Press

### *General Physiology*

- 10 Textbook of Medical Physiology 9<sup>th</sup> Edition by A.C. Guyton and J.E. Hall W.B. Saunders, 1997; Review of Medical Physiology, 18<sup>th</sup> Edition by W.F. Ganong, Appleton and Lange, 1997.

### *Online Databases*

- Those skilled in the art are familiar with how to search the biomedical literature, such as, e.g., libraries, online PubMed, abstract listings, and online  
15 mutation databases. One particularly useful resource is maintained at the web site of the National Center for Biotechnology Information (ncbi):  
<http://www.ncbi.nlm.nih.gov/>. From the ncbi site one can access Online Mendelian Inheritance in Man (OMIM),. OMIM can be found at:  
<http://www3.ncbi.nlm.nih.gov/Omim/searchomim.html>. OMIM is a medically  
20 oriented database of genetic information with entries for thousands of genes. The OMIM record number is provided for many of the genes in Tables 1-6 and 12-23 (see column 3), and constitutes an excellent entry point for identification of references that point to the broader literature. Another useful site at NCBI is the Entrez browser, located at <http://www3.ncbi.nlm.nih.gov/Entrez/>. One can search  
25 genomes, polynucleotides, proteins, 3D structures, taxonomy or the biomedical literature (PubMed) via the Entrez site. More generally links to a number of useful sites with biomedical or genetic data are maintained at sites such as Med Web at the Emory University Health Sciences Center Library:  
<http://WWW.MedWeb.Emory.Edu/MedWeb/>; Riken, a Japanese web site at:  
30 <http://www.rtc.riken.go.jp/othersite.html> with links to DNA sequence, structural, molecular biology, bioinformatics, and other databases; at the Oak Ridge National Laboratory web site: <http://www.ornl.gov/hgmis/links.html>; or at the Yahoo website of Diseases and Conditions:  
[http://dir.yahoo.com/health/diseases\\_and\\_conditions/index.html](http://dir.yahoo.com/health/diseases_and_conditions/index.html). Each of the  
35 indicated web sites has additional useful links to other sites.

Another type of database with utility in selecting the genes on a biochemical pathway that may affect the response to a drug are databases that provide information on biochemical pathways. Examples of such databases include the Kyoto Encyclopedia of Genes and Genomes (KEGG), which can be found at:

5 <http://www.genome.ad.jp/kegg/kegg.html>. This site has pictures of many biochemical pathways, as well as links to other metabolic databases such as the well known Boehringer Mannheim biochemical pathways charts:

<http://www.expasy.ch/cgi-bin/search-biochem-index>. The metabolic charts at the latter site are comprehensive, and excellent starting points for working out the salient enzymes on any given pathway.

Each of the web sites mentioned above has links to other useful web sites, which in turn can lead to additional sites with useful information. *Research Libraries*

Those skilled in the art will often require information found only at large libraries. The National Library of Medicine (<http://www.nlm.nih.gov/>) is the largest medical library in the world and its catalogs can be searched online. Other libraries, such as university or medical school libraries are also useful to conduct searches. Biomedical books such as those referred to above can often be obtained from online bookstores as described above.

#### *Biomedical Literature*

20 To obtain up to date information on drugs and their mechanism of action and biotransformation; disease pathophysiology; biochemical pathways relevant to drug action and disease pathophysiology; and genes that encode proteins relevant to drug action and disease one skilled in the art will consult the biomedical literature. A widely used, publically accessible web site for searching published journal articles is PubMed (<http://www.ncbi.nlm.nih.gov/PubMed/>). At this site, one can search for the most recent articles (within the last 1-2 months) or older literature (back to 1966). Many Journals also have their own sites on the world wide web and can be searched online. For example see the IDEAL web site at: <http://www.apnet.com/www/ap/aboutid.html>. This site is an online library, featuring full text journals from Academic Press and selected journals from W.B. Saunders and Churchill Livingstone. The site provides access (for a fee) to nearly 2000 scientific, technical, and medical journals.

*Experimental methods for identification of genes involved in the action of a drug*



There are a number of experimental methods for identifying genes and gene products that mediate or modulate the effects of a drug or other treatment. They encompass analyses of RNA and protein expression as well as methods for detecting protein – protein interactions and protein – ligand interactions. Two preferred ,  
5 experimental methods for identification of genes that may be involved in the action of a drug are (1) methods for measuring the expression levels of many mRNA transcripts in cells or organisms treated with the drug (2) methods for measuring the expression levels of many proteins in cells or organisms treated with the drug.

RNA transcripts or proteins that are substantially increased or decreased in  
10 drug treated cells or tissues relative to control cells or tissues are candidates for mediating the action of the drug. Preferably the level of an mRNA is at least 30% higher or lower in drug treated cells, more preferably at least 50% higher or lower, and most preferably two fold higher or lower than levels in non-drug treated control cells. The analysis of RNA levels can be performed on total RNA or on  
15 polyadenylated RNA selected by oligodT affinity. Further, RNA from different cell compartments can be analyzed independently – for example nuclear vs. cytoplasmic RNA. In addition to RNA levels, RNA kinetics can be examined, or the pool of RNAs currently being translated can be analyzed by isolation of RNA from polysomes. Other useful experimental methods include protein interaction methods  
20 such as the yeast two hybrid system and variants thereof which facilitate the detection of protein – protein interactions. Preferably one of the interacting proteins is the drug target or another protein strongly implicated in the action of the compound being assessed.

The pool of RNAs expressed in a cell is sometimes referred to as the  
25 transcriptome. Methods for measuring the transcriptome, or some part of it, are known in the art. A recent collection of articles summarizing some current methods appeared as a supplement to the journal *Nature Genetics*. (The Chipping Forecast. *Nature Genetics* supplement, volume 21, January 1999.) A preferred method for measuring expression levels of mRNAs is to spot PCR products corresponding to a  
30 large number of specific genes on a nylon membrane such as Hybond N Plus (Amersham-Pharmacia). Total cellular mRNA is then isolated, labelled by random oligonucleotide priming in the presence of a detectable label (e.g. alpha 33P labelled radionucleotides or dye labelled nucleotides), and hybridized with the filter containing the PCR products. The resulting signals can be analyzed by  
35 commercially available software, such as can be obtained from Clontech/Molecular Dynamics or Research Genetics, Inc.

Experiments have been described in model systems that demonstrate the utility of measuring changes in the transcriptome before and after changing the growth conditions of cells, for example by changing the nutrient environment. The changes in gene expression help reveal the network of genes that mediate physiological responses to the altered growth condition. Similarly, the addition of a drug to the cellular or in vivo environment, followed by monitoring the changes in gene expression can aid in identification of gene networks that mediate pharmacological responses.

The pool of proteins expressed in a cell is sometimes referred to as the proteome. Studies of the proteome may include not only protein abundance but also protein subcellular localization and protein-protein interaction. Methods for measuring the proteome, or some part of it, are known in the art. One widely used method is to extract total cellular protein and separate it in two dimensions, for example first by size and then by isoelectric point. The resulting protein spots can be stained and quantitated, and individual spots can be excised and analyzed by mass spectrometry to provide definitive identification. The results can be compared from two or more cell lines or tissues, at least one of which has been treated with a drug. The differential up or down modulation of specific proteins in response to drug treatment may indicate their role in mediating the pharmacologic actions of the drug. Another way to identify the network of proteins that mediate the actions of a drug is to exploit methods for identifying interacting proteins. By starting with a protein known to be involved in the action of a drug – for example the drug target – one can use systems such as the yeast two hybrid system and variants thereof (known to those skilled in the art; see Ausubel et al., Current Protocols in Molecular Biology, op. cit.) to identify additional proteins in the network of proteins that mediate drug action. The genes encoding such proteins would be useful for screening for DNA sequence variances, which in turn may be useful for analysis of interpatient variation in response to treatments. For example, the protein 5-lipoxygenase (5LO) is an enzyme which is at the beginning of the leukotriene biosynthetic pathway and is a target for anti-inflammatory drugs used to treat asthma and other diseases. In order to detect proteins that interact with 5-lipoxygenase the two-hybrid system was recently used to isolate three different proteins, none previously known to interact with 5LO. (Provost et al., Interaction of 5-lipoxygenase with cellular proteins. *Proc. Natl. Acad. Sci. U.S.A.* 96: 1881-1885, 1999.) A recent collection of articles summarizing some current methods in proteomics appeared in the August 1998 issue of the journal *Electrophoresis* (volume 19, number 11). Other useful articles include: Blackstock WP, et al.

Proteomics: quantitative and physical mapping of cellular proteins. *Trends Biotechnol.* 17 (3): p. 121-7, 1999, and Patton W.F., Proteome analysis II. Protein subcellular redistribution: linking physiology to genomics via the proteome and separation technologies involved. *J Chromatogr B Biomed Sci App.* 722(1-2):203-23. 1999.

Since many of these methods can also be used to assess whether specific polymorphisms are likely to have biological effects, they are also relevant in section 3, below, concerning methods for assessing the likely contribution of variances in candidate genes to clinical variation in patient responses to therapy.

## 2. Screen for Variances in Genes that may be Related to Therapeutic Response

Having identified a set of genes that may affect response to a drug the next step is to screen the genes for variances that may account for interindividual variation in response to the drug. There are a variety of levels at which a gene can be screened for variances, and a variety of methods for variance screening. The two main levels of variance screening are genomic DNA screening and cDNA screening. Genomic variance detection may include screening the entire genomic segment spanning the gene from 2 kb to 10 kb upstream of the transcription start site to the polyadenylation site, or 2 to 10 kb beyond the polyadenylation site. Alternatively genomic variance detection may (for intron containing genes) include the exons and some region around them containing the splicing signals, for example, but not all of the intronic sequences. In addition to screening introns and exons for variances it is generally desirable to screen regulatory DNA sequences for variances. Promoter, enhancer, silencer and other regulatory elements have been described in human genes. The promoter is generally proximal to the transcription start site, although there may be several promoters and several transcription start sites. Enhancer, silencer and other regulatory elements may be intragenic or may lie outside the introns and exons, possibly at a considerable distance, such as 100 kb away. Variances in such sequences may affect basal gene expression or regulation of gene expression. In either case such variation may affect the response of an individual patient to a therapeutic intervention, for example a drug, as described in the examples. Thus in practicing the present invention it is useful to screen regulatory sequences as well as transcribed sequences, in order to identify variances that may affect gene transcription. Frequently the genomic sequence of a gene can be found in the sources above, particularly by searching GenBank or Medline (PubMed). The name of the gene can be entered at a site such as Entrez: <http://www.ncbi.nlm.nih.gov/Entrez/nucleotide.html>. Using the genomic sequence

and information from the biomedical literature one skilled in the art can perform a variance detection procedure such as those described in examples 2, 3, 4.

Variance detection is often first performed on the cDNA of a gene for several reasons. First, available data on functional sequence variances suggests that  
5 variances in the transcribed portion of a gene may be most likely to have functional consequences as they can affect the interaction of the transcript with a wide variety of cellular factors during the complex processes of RNA transcription, processing and translation, with consequent effects on RNA splicing, stability, translational efficiency or other processes. Second, as a practical matter the cDNA sequence of a  
10 gene is often available before the genomic structure is known, although the reverse will be true in the future as the sequence of the human genome is determined. Third, the cDNA is often compact compared to the genomic locus, and can be screened for variances with much less effort. If the genomic structure is not known then only the cDNA sequence can be scanned for variances. Methods for preparing cDNA are  
15 described in Example 1. Methods for variance detection on cDNA are described below and in the examples.

In general it is preferable to catalog genetic variation at the genomic DNA level because there are an increasing number of well documented instances of functionally important variances that lie outside of transcribed sequence. Also, to  
20 properly use optimal genetic methods to assess the contribution of a candidate gene to variation in a phenotype of interest it is desirable to understand the character of sequence variation in the candidate gene: what is the nature of linkage disequilibrium between different variances in the gene; are there sites of recombination within the gene; what is the extent of homoplasy in the gene (i.e.  
25 occurrence of two variant sites that are identical by state but not identical by descent because the same variance arose at least twice in human evolutionary history on two different haplotypes); what are the different haplotypes and how can they be grouped to increase the power of genetic analysis?

Methods for variance screening have been described, including DNA  
30 sequencing. See for example: US5698400: Detection of mutation by resolvase cleavage; US5217863: Detection of mutations in nucleic acids; and US5750335: Screening for genetic variation, as well as the examples and references cited therein for examples of useful variance detection procedures. Detailed variance detection procedures are also described in examples 2, 3, 4. One skilled in the art will  
35 recognize that depending on the specific aims of a variance detection project (number of genes being screened, number of individuals being screened, total length

of DNA being screened) one of the above cited methods may be preferable to the others, or yet another procedure may be optimal. A preferred method of variance detection is chain terminating DNA sequencing using dye labeled primers, cycle sequencing and software for assessing the quality of the DNA sequence as well as specialized software for calling heterozygotes. The use of such procedures has been described by Nickerson and colleagues. See for example: Rieder M.J., et al. Automating the identification of DNA variations using quality-based fluorescence re-sequencing: analysis of the human mitochondrial genome. *Nucleic Acids Res.* 26 (4):967-73, 1998. and: Nickerson D.A., et al. PolyPhred: automating the detection and genotyping of single nucleotide substitutions using fluorescence-based resequencing. *Nucleic Acids Res.* 25 (14):2745-51, 1997. Although the variances provided in Tables 12-17, and 18-23 consist principally of cDNA variances, it is an aspect of this invention that detection of genomic variances is also a useful method for identification of variances that may account for interpatient variation in response to a therapy.

Another important aspect of variance detection is the use of DNA from a panel of human subjects that represents a known population. For example, if the subjects are being screened for variances relevant to a specific drug development program it is desirable to include both subjects with the target disease and healthy subjects in the panel, because certain variances may occur at different frequencies in the healthy and disease populations and can only be reliably detected by screening both populations. Also, for example, if the drug development program is taking place in Japan, it is important to include Japanese individuals in the screening population. In general, it is always desirable to include subjects of known geographic, racial or ethnic identity in a variance screening experiment so the results can be interpreted appropriately for different patient populations, if necessary. Also, in order to select optimal sets of variances for genetic analysis of a gene locus it is desirable to know which variances have occurred recently – perhaps on multiple different chromosomes - and which are ancient. Inclusion of one or more apes or monkeys in the variance screening panel is one way of gaining insight into the evolutionary history of variances. Chimpanzees are preferred subjects for inclusion in a variance screening panel.

### 3. Assess the Likely Contribution of Variances in Candidate Genes to Clinical Variation in Patient Responses to Therapy

Once a set of genes likely to affect disease pathophysiology or drug action has been identified, and those genes have been screened for variances, said variances

(e.g., provided in Tables 12-17, and 18-23) can be assessed for their contribution to variation in the pharmacological or toxicological phenotypes of interest. Such studies are useful for reducing a large number of candidate variances to a smaller number of variances to be tested in clinical trials. There are several methods which can be used in the present invention for assessing the medical and pharmaceutical implications of a DNA sequence variance. They range from computational methods to *in vitro* and/or *in vivo* experimental methods, to prospective human clinical trials, and also include a variety of other laboratory and clinical measures that can provide evidence of the medical consequences of a variance. In general, human clinical trials constitute the highest standard of proof that a variance or set of variances is useful for selecting a method of treatment, however, computational and *in vitro* data, or retrospective analysis of human clinical data may provide strong evidence that a particular variance will affect response to a given therapy, often at lower cost and in less time than a prospective clinical trial. Moreover, at an early stage in the analysis when there are many possible hypotheses to explain interpatient variation in treatment response, the use of informatics-based approaches to evaluate the likely functional effects of specific variances is an efficient way to proceed.

Informatics-based approaches to the prediction of the likely functional effects of variances include DNA and protein sequence analysis (phylogenetic approaches and motif searching) and protein modeling (based on coordinates in the protein database, or pdb; see <http://www.rcsb.org/pdb/>). See, for example: Kawabata et al. The Protein Mutant Database. *Nucleic Acids Research* 27: 355-357, 1999; also available at: <http://pmd.ddbj.nig.ac.jp>. Such analyses can be performed quickly and inexpensively, and the results may allow selection of certain genes for more extensive *in vitro* or *in vivo* studies or for more variance detection or both.

The three dimensional structure of many medically and pharmaceutically important proteins, or homologs of such proteins in other species, or examples of domains present in such proteins, is known as a result of x-ray crystallography studies and, increasingly, nuclear magnetic resonance studies. Further, there are increasingly powerful tools for modeling the structure of proteins with unsolved structure, particularly if there is a related (homologous) protein with known structure. (For reviews see: Rost et al., Protein fold recognition by prediction-based threading, *J. Mol. Biol.* 270:471-480, 1997; Firestine et al., Threading your way to protein function, *Chem. Biol.* 3:779-783, 1996) There are also powerful methods for identifying conserved domains and vital amino acid residues of proteins of unknown structure by analysis of phylogenetic relationships. (Deleage et al., Protein structure prediction: Implications for the biologist, *Biochimie* 79:681-686, 1997; Taylor et al., Multiple protein structure alignment, *Protein Sci.* 3:1858-1870, 1994) These

methods can permit the prediction of functionally important variances, either on the basis of structure or evolutionary conservation. For example, a crystal structure can reveal which amino acids comprise a small molecule binding site. The identification of a polymorphic amino acid variance in the topological neighborhood of such a site, and, in particular, the demonstration that at least one variant form of the protein has a variant amino acid which impinges on (or which may otherwise affect the chemical environment around) the small molecule binding pocket differently from another variant form, provides strong evidence that the variance may affect the function of the protein. From this it follows that the interaction of the protein with a treatment method, such as an administered compound, will likely be variable between different patients. One skilled in the art will recognize that the application of computational tools to the identification of functionally consequential variances involves applying the knowledge and tools of medicinal chemistry and physiology to the analysis.

Phylogenetic approaches to understanding sequence variation are also useful. Thus if a sequence variance occurs at a nucleotide or encoded amino acid residue where there is usually little or no variation in homologs of the protein of interest from non-human species, particularly evolutionarily remote species, then the variance is more likely to affect function of the RNA or protein. Computational methods for phylogenetic analysis are known in the art, (see below for citations of some methods).

Computational methods are also useful for analyzing DNA polymorphisms in transcriptional regulatory sequences, including promoters and enhancers. One useful approach is to compare variances in potential or proven transcriptional regulatory sequences to a catalog of all known transcriptional regulatory sequences, including consensus binding domains for all transcription factor binding domains. See, for example, the databases cited in: Burks, C. *Molecular Biology Database List. Nucleic Acids Research* 27: 1-9, 1999, and links to useful databases on the internet at:

[http://www.oup.co.uk/nar/Volume\\_27/issue\\_01/summary/gkc105\\_gml.html](http://www.oup.co.uk/nar/Volume_27/issue_01/summary/gkc105_gml.html). In particular see the Transcription Factor Database (Heinemeyer, T., et al. (1999) Expanding the TRANSFAC database towards an expert system of regulatory molecular mechanisms. *Nucleic Acids Res.* 27: 318-322, or on the internet at: <http://193.175.244.40/TRANSFAC/index.html>). Any sequence variances in transcriptional regulatory sequences can be assessed for their effects on mRNA levels using standard methods, either by making plasmid constructs with the different allelic forms of the sequence, transfecting them into cells and measuring the output of a reporter transcript, or by assays of cells with different endogenous

alleles of variances. One example of a polymorphism in a transcriptional regulatory element that has a pharmacogenetic effect is described by Drazen et al. (1999) Pharmacogenetic association between ALOX5 promoter genotype and the response to anti-asthma treatment. *Nature Genetics* 22: 168-170. Drazen and co-workers  
5 found that a polymorphism in an Sp1-transcription factor binding domain, which varied among subjects from 3-6 tandem copies, accounted for varied expression levels of the 5-lipoxygenase gene when assayed in vitro in reporter construct assays. This effect would have been flagged by an informatics analysis that surveyed the 5-lipoxygenase candidate promoter region for transcriptional regulatory sequences  
10 (resulting in discovery of polymorphism in the Sp1 motif).

#### 4. Perform *in vitro* or *in vivo* Experiments to Assess the Functional Importance of Gene Variances

There are two broad types of studies useful for assessing the likely  
15 importance of variances: analysis of RNA or protein abundance (as described above in the context of methods for identifying candidate genes for explaining interpatient variation in treatment response) or analysis of functional differences in different variant forms of a gene, mRNA or protein. Studies of functional differences may involve direct measurements of biochemical activity of different variant forms of an  
20 mRNA or protein, or may involve assaying the influence of a variance or variances on various cell properties, including both tissue culture and *in vivo* studies.

The selection of an appropriate experimental program for testing the medical consequences of a variance may differ depending on the nature of the variance, the gene, and the disease. For example if there is already evidence that a protein is  
25 involved in the pharmacologic action of a drug, then the *in vitro* or *in vivo* demonstration that an amino acid variance in the protein affects its biochemical activity is strong evidence that the variance will have an effect on the pharmacology of the drug in patients, and therefore that patients with different variant forms of the gene may have different responses to the same dose of drug. If the variance is silent  
30 with respect to protein coding information, or if it lies in a noncoding portion of the gene (e.g., a promoter, an intron, or a 5'- or 3'-untranslated region) then the appropriate biochemical assay may be to assess mRNA abundance, half life, or translational efficiency. If, on the other hand, there is no substantial evidence that the protein encoded by a particular gene is relevant to drug pharmacology, but  
35 instead is a candidate gene on account of its involvement in disease pathophysiology, then the optimal test may be a clinical study addressing whether two patient groups distinguished on the basis of the variance respond differently to a therapeutic intervention. This approach reflects the current reality that biologists do



not sufficiently understand gene regulation, gene expression and gene function to consistently make accurate inferences about the consequences of DNA sequence variances for pharmacological responses.

In summary, if there is a plausible hypothesis regarding the effect of a protein on the action of a drug, then *in vitro* and *in vivo* approaches, including those described below, will be useful to predict whether a given variance is therapeutically consequential. If, on the other hand, there is no evidence of such an effect, then the preferred test is an empirical clinical measure of the impact to the variance on efficacy or toxicity *in vivo* (which requires no evidence or assumptions regarding the mechanism by which the variance may exert an effect on a therapeutic response). However, given the expense and statistical constraints of clinical trials, it is preferable to limit clinical testing to variances for which there is at least some experimental or computational evidence of a functional effect.

#### *Experimental Methods: Genomic DNA Analysis*

Variances in DNA may affect the basal transcription or regulated transcription of a gene locus. Such variances may be located in any part of the gene but are most likely to be located in the promoter region, the first intron, or in 5' or 3' flanking DNA, where enhancer or silencer elements may be located. Methods for analyzing transcription are well known to those skilled in the art and exemplary methods are briefly described above and in some of the texts cited elsewhere in this application. Transcriptional run off assay is one useful method. Detailed protocols can be found in texts such as: Current Protocols in Molecular Biology edited by: F.M. Ausubel, et al. John Wiley & Sons, Inc, 1999, or: Molecular Cloning: A Laboratory Manual by J. Sambrook, E.F. Fritsch and T Maniatis. 1989. 3 vols, 2nd edition, Cold Spring Harbor Laboratory Press

#### *Experimental Methods: RNA Analysis*

RNA variances may affect a wide range of processes including RNA splicing, polyadenylation, capping, export from the nucleus, interaction with translation initiation, elongation or termination factors, or the ribosome, or interaction with cellular factors including regulatory proteins, or factors that may affect mRNA half life. However, the effect of most RNA sequence variances on RNA function, if any, should ultimately be measurable as an effect on RNA or protein levels – either basal levels or regulated levels or levels in some abnormal cell state, such as cells from patients with a disease. Therefore, one preferred method for assessing the effect of RNA variances on RNA function is to measure the levels of RNA produced by different alleles in one or more conditions of cell or tissue

growth. Said measuring can be done by conventional methods such as Northern blots or RNAase protection assays (kits available from Ambion, Inc.), or by methods such as the Taqman assay (developed by the Applied Biosystems Division of the Perkin Elmer Corporation), or by using arrays of oligonucleotides or arrays of cDNAs attached to solid surfaces. Systems for arraying cDNAs are available commercially from companies such as Nanogen and General Scanning. Complete systems for gene expression analysis are available from companies such as Molecular Dynamics. For recent reviews of systems for high throughput RNA expression analysis see the supplement to volume 21 of Nature Genetics entitled "The Chipping Forecast", especially articles beginning on pages 9, 15, 20 and 25.

Additional methods for analyzing the effect of variances on RNA include secondary structure probing, and direct measurement of half life or turnover. Secondary structure can be determined by techniques such as enzymatic probing (using enzymes such as T1, T2 and S1 nuclease), chemical probing or RNAase H probing using oligonucleotides. Most RNA structural assays are performed *in vitro*, however some techniques can be performed on cell extracts or even in living cells, using fluorescence resonance energy transfer to monitor the state of RNA probe molecules.

#### *Experimental Methods: Protein Analysis*

There are a variety of experimental methods for investigating the effect of an amino acid variance on response of a patient to a treatment. The preferred method will depend on the availability of cells expressing a particular protein, and the feasibility of a cell-based assay vs. assays on cell extracts, on proteins produced in a foreign host, or on proteins prepared by *in vitro* translation.

For example, the methods and systems listed below can be utilized to demonstrate differential expression, stability and/or activity of different variant forms of a protein, or in phenotype/genotype correlations in a model system.

For the determination of protein levels or protein activity a variety of techniques are available. The *in vitro* protein activity can be determined by transcription or translation in bacteria, yeast, baculovirus, COS cells (transient), Chinese Hamster Ovary (CHO) cells, or studied directly in human cells, or other cell systems can be used. Further, one can perform pulse chase experiments to determine if there are changes in protein stability (half-life).

One skilled in the art can construct cell based assays of protein function, and then perform the assays in cells with different genotypes or haplotypes. For example, identification of cells with different genotypes, e.g. cell lines established from families and subsequent determination of relevant protein phenotypes (e.g.

expression levels, post translational modifications, activity assays) may be performed using standard methods.

Assays of protein levels or function can also be performed on cell lines (or extracts from cell lines) derived from pedigrees in order to determine whether there is a genetic component to variation in protein levels or function. The experimental analysis is as above for RNAs, except the assays are different. Experiments can be performed on naive cells or on cells subjected to various treatments, including pharmacological treatments.

In another approach to the study of amino acid variances one can express genes corresponding to different alleles in experimental organisms and examine effects on disease phenotype (if relevant in the animal model), or on response to the presence of a compound. Such experiments may be performed in animals that have disrupted copies of the homologous gene (e.g. gene knockout animals engineered to be deficient in a target gene), or variant forms of the human gene may be introduced into germ cells by transgenic methods, or a combination of approaches may be used. To create animal strains with targeted gene disruptions a DNA construct is created (using DNA sequence information from the host animal) that will undergo homologous recombination when inserted into the nucleus of an embryonic stem cell. The targeted gene is effectively inactivated due to the insertion of non-natural sequence – for example a translation stop codon or a marker gene sequence that interrupts the reading frame. Well known PCR based methods are then used to screen for those cells in which the desired homologous recombination event has occurred. Gene knockouts can be accomplished in worms, drosophila, mice or other organisms. Once the knockout cells are created (in whatever species) the candidate therapeutic intervention can be administered to the animal and pharmacological or biological responses measured, including gene expression levels. If variant forms of the gene are useful in explaining interpatient variation in response to the compound in man, then complete absence of the gene in an experimental organism should have a major effect on drug response. As a next step various human forms of the gene can be introduced into the knockout organism (a technique sometimes referred to as a knock-in). Again, pharmacological studies can be performed to assess the impact of different human variances on drug response. Methods relevant to the experimental approaches described above can be found in the following exemplary texts:

*General Molecular Biology Methods*

Molecular Biology: A project approach, S.J. Karcher, Fall 1995. Academic Press; DNA Cloning: A Practical Approach, D.M. Glover and B.D. Hayes (eds). 1995. IRL/Oxford University Press. Vol. 1 - Core Techniques; Vol 2 - Expression Systems; Vol. 3 -

Complex Genomes; Vol. 4 -Mammalian Systems; Short Protocols in Molecular Biology, Ausubel et al. October 1995. 3rd edition, John Wiley and Sons; Current Protocols in Molecular Biology Edited by: F.M. Ausubel, R.Brent, R.E. Kingston, D.D. Moore, J.G. Seidman, K. Struhl, (Series Editor: V.B. Chanda), 1988; Molecular Cloning: A laboratory manual, J. Sambrook, E.F. Fritsch. 1989. 3 vols, 2nd edition, Cold Spring Harbor Laboratory Press.

*Polymerase chain reaction (PCR)*

PCR Primer: A laboratory manual, C.W. Diffenbach and G.S. Dveksler (eds.). 1995. Cold Spring Harbor Laboratory Press; The Polymerase Chain Reaction, K.B. Mullis et al. (eds.), 1994. Birkhauser; PCR Strategies, M.A. Innis, D.H. Gelf, and J.J. Sninsky (eds.), 1995. Academic Press.

*General procedures for discipline specific studies*

Current Protocols in Neuroscience Edited by: J. Crawley, C. Gerfen, R. McKay, M. Rogawski, D. Sibley, P. Skolnick, (Series Editor: G. Taylor), 1997; Current Protocols in Pharmacology Edited by: S. J. Enna / M. Williams, J.W. Ferkany, T. Kenakin, R.E. Porsolt, J.P. Sullivan, (Series Editor: G. Taylor), 1998; Current Protocols in Protein Science Edited by: J.E. Coligan, B.M. Dunn, H.L. Ploegh, D.W. Speicher, P.T. Wingfield, (Series Editor: Virginia Benson Chanda), 1995; Current Protocols in Cell Biology Edited by: J.S. Bonifacino, M. Dasso, J. Lippincott-Schwartz, J.B. Harford, K.M. Yamada, (Series Editor: K. Morgan) 1999; Current Protocols in Cytometry Managing Editor: J.P. Robinson, Z. Darzynkiewicz (ed) / P. Dean (ed), A. Orfao (ed), P. Rabinovitch (ed), C. Stewart (ed), H. Tanke (ed), L. Wheelless (ed), (Series Editor: J. Paul Robinson), 1997; Current Protocols in Human Genetics Edited by: N.C. Dracopoli, J.L. Haines, B.R. Korf, et al., (Series Editor: A. Boyle), 1994; Current Protocols in Immunology Edited by: J.E. Coligan, A.M. Kruisbeek, D.H. Margulies, E.M. Shevach, W. Strober, (Series Editor: R. Coico), 1991.

IV. Clinical Trials

A clinical trial is the definitive test of the utility of a variance or variances for the selection of optimal therapy. A clinical trial in which an interaction of gene variances and clinical outcomes (desired or undesired) is explored will be referred to herein as a "pharmacogenetic clinical trial". Pharmacogenetic clinical trials require no knowledge of the biological function of the gene containing the variance or variances to be assessed, nor any knowledge of how the therapeutic intervention to be assessed works at a biochemical level. The pharmacogenetics effects of a variance can be addressed at a purely statistical level: either a particular variance or

set of variances is consistently associated with a significant difference in a salient drug response parameter (e.g. response rate, effective dose, side effect rate, etc.) or not. On the other hand, if there is information about either the biochemical basis of a therapeutic intervention or the biochemical effects of a variance, then a  
5 pharmacogenetic clinical trial can be designed to test a specific hypothesis. In preferred embodiments of the methods of this application the mechanism of action of the compound to be genetically analyzed is at least partially understood.

Methods for performing clinical trials are well known in the art. (see e.g. Guide to Clinical Trials by Bert Spilker, Raven Press, 1991; The Randomized  
10 Clinical Trial and Therapeutic Decisions by Niels Tygstrup (Editor), Marcel Dekker; Recent Advances in Clinical Trial Design and Analysis (Cancer Treatment and Research, Ctar 75) by Peter F. Thall (Editor) Kluwer Academic Pub, 1995. Clinical Trials: A Methodologic Perspective by Steven Piantadosi, Wiley Series in Probability and Statistics, 1997). However, performing a clinical trial to test the  
15 genetic contribution to interpatient variation in drug response entails additional design considerations, including (i) defining the genetic hypothesis or hypotheses, (ii) devising an analytical strategy for testing the hypothesis, including determination of how many patients will need to be enrolled to have adequate statistical power to measure an effect of a specified magnitude (power analysis), (iii)  
20 definition of any primary or secondary genetic endpoints, and (iv) definition of methods of statistical genetic analysis, as well as other aspects. In the outline below some of the major types of genetic hypothesis testing, power analysis and statistical testing and their application in different stages of the drug development process are reviewed. One skilled in the art will recognize that certain of the methods will be  
25 best suited to specific clinical situations, and that additional methods are known and can be used in particular instances.

#### A. *Performing a Clinical Trial: Overview*

As used herein, a "clinical trial" is the testing of a therapeutic intervention in  
30 a volunteer human population for the purpose of determining whether it is safe and/or efficacious in the treatment of a disease, disorder, or condition. The present invention describes methods for achieving superior efficacy and/or safety in a genetically defined subgroup defined by the presence or absence of at least one gene sequence variance, compared to the effect that could be obtained in a conventional  
35 trial (without genetic stratification).

A "clinical study" is that part of a clinical trial that involves determination of the effect of a candidate therapeutic intervention on human subjects. It includes clinical evaluation of physiologic responses including pharmacokinetic (bioavailability as affected by drug absorption, distribution, metabolism and excretion) and pharmacodynamic (physiologic response and efficacy) parameters. A pharmacogenetic clinical study (or clinical trial) is a clinical study that involves testing of one or more specific hypotheses regarding the interaction of a genetic variance or variances (or set of variances, i.e. haplotype or haplotypes) on response to a therapeutic intervention. Pharmacogenetic hypotheses are formulated before the study, and may be articulated in the study protocol in the form of primary or secondary endpoints. For example an endpoint may be that in a particular genetic subgroup the rate of objectively defined responses exceeds the response rate in a control group (either the entire control group or the subgroup of controls with the same genetic signature as the treatment subgroup they are being compared to) or exceeds that in the whole treatment group (i.e. without genetic stratification) by some predefined relative or absolute amount.

For a clinical study to commence enrollment and proceed to treat subjects at an institution that receives any federal support (most medical institutions in the US), an application that describes in detail the scientific premise for the therapeutic intervention and the procedures involved in the study, including the endpoints and analytical methods to be used in evaluating the data, must be reviewed and accepted by a review panel, often termed an Institutional Review Board (IRB). Similarly any clinical study that will ultimately be evaluated by the FDA as part of a new drug or product application (or other application as described below), must be reviewed and approved by an IRB. The IRB is responsible for determining that the trial protocol is safe, conforms to established ethical principles and guidelines, has risks proportional to any expected benefits, assures equitable selection of patients, provides sufficient information to patients (via a consent form) to insure that they can make an informed decision about participation, and insures the privacy of participants and the confidentiality of any data collected. (See the report of the National Commission for Protection of Human Subjects of Biomedical and Behavioral Research (1978). The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research. Washington, D.C.: DHEW Publication Number (OS) 78-0012. For a recent review see: Coughlin, S.S. (ed.) (1995) Ethics in Epidemiology and Clinical Research. Epidemiology Resources, Newton, MA.) The European counterpart of the US FDA is the European Medicines Evaluation Agency (EMA). Similar agencies exist in other

countries and are responsible for insuring, via the regulatory process, that clinical trials conform to similar standards as are required in the US. The documents reviewed by an IRB include a clinical protocol containing the information described above, and a consent form.

5 It is also customary, but not required, to prepare an investigator's brochure which describes the scientific hypothesis for the proposed therapeutic intervention, the preclinical data, and the clinical protocol. The brochure is made available to any physician participating in the proposed or ongoing trial.

10 The supporting preclinical data is a report of all the *in vitro*, *in vivo* animal or previous human trial or other data that supports the safety and/or efficacy of a given therapeutic intervention. In a pharmacogenetic clinical trial the preclinical data may also include a description of the effect of a specific genetic variance or variances on biochemical or physiologic experimental variables *in vitro* or *in vivo*, or on treatment outcomes, as determined by *in vivo* studies in animals or humans (for example in an  
15 earlier trial), or by retrospective genetic analysis of clinical trial or other medical data (see below) used to formulate or strengthen a pharmacogenetic hypothesis. For example, case reports of unusual pharmacological responses in individuals with rare alleles (e.g. mutant alleles), or the observation of clustering of pharmacological responses in family members may provide the rationale for a pharmacogenetic  
20 clinical trial.

The clinical protocol provides the relevant scientific and therapeutic introductory information, describes the inclusion and exclusion criteria for human subject enrollment, including genetic criteria if relevant (e.g. if genotype is to be among the enrollment criteria), describes in detail the exact procedure or procedures  
25 for treatment using the candidate therapeutic intervention, describes laboratory analyses to be performed during the study period, and further describes the risks (both known and possible) involving the use of the experimental candidate therapeutic intervention. In a clinical protocol for a pharmacogenetic clinical trial, the clinical protocol will further describe the genetic variance and/or variances  
30 hypothesized to account for differential responses in the normal human subjects or patients and supporting preclinical data, if any, a description of the methods for genotyping, genetic data collection and data handling as well as a description of the genetic statistical analysis to be performed to measure the interaction of the variance or variances with treatment response. Further, the clinical protocol for a  
35 pharmacogenetic clinical trial will include a description of the genetic study design. For example patients may be stratified by genotype and the response rates in the different groups compared, or patients may be segregated by response and the genotype frequencies in the different responder or nonresponder groups measured.

One or more gene sequence variances or a combination of variances and/or haplotypes may be studied.

The informed consent document is a description of the therapeutic intervention and the clinical protocol in simple language (e.g. third grade level) for the patient to read, understand, and, if willing, agree to participate in the study by signing the document. In a pharmacogenetic clinical study the informed consent document will describe, in simple language, the use of a genetic test or a limited set of genetic tests to determine the subject or patient's genotype at a particular gene variance or variances, and to further ascertain whether, in the study population, particular variances are associated with particular clinical or physiological responses. The consent form should also describe procedures for assuring privacy and confidentiality of genetic information.

The US FDA reviews proposed clinical trials through the process of an Investigational New Drug Application (IND). The IND is composed of the investigator's brochure, the supporting *in vitro* and *in vivo* animal or previous human data, the clinical protocol, and the informed consent forms. In each of the sections of the IND, a specific description of a single allelic variance or a number of variances to be tested in the clinical study will be included. For example, in the investigator's brochure a description of the gene or genes hypothesized to account, at least in part, for differential responses will be included as well as a description of a genetic variance or variances in one or more candidate genes. Further, the preclinical data may include a description of *in vivo*, *in vitro* or *in silico* studies of the biochemical or physiologic effects of a variance or variances (e.g., haplotype) in a candidate gene or genes, as well as the predicted effects of the variance or variances on efficacy or toxicology of the candidate therapeutic intervention. The results of retrospective genetic analysis of response data in patients treated with the candidate therapy may be the basis for formulating the genetic hypotheses to be tested in the prospective trial. The US FDA reviews applications with particular attention to safety and toxicological data to ascertain whether candidate compounds should be tested in humans.

The established phases of clinical development are Phase I, II, III, and IV. The fundamental objectives for each phase become increasingly complex as the stages of clinical development progress. In Phase I, safety in humans is the primary focus. In these studies, dose-ranging designs establish whether the candidate therapeutic intervention is safe in the suspected therapeutic concentration range. However, it is common practice to obtain information about surrogate markers of efficacy even in phase I clinical trials. In a pharmacogenetic clinical trial there may be an analysis of the effect of a variance or variances on Phase I safety or surrogate



efficacy parameters. At the same time, evaluation of pharmacokinetic parameters (e.g., adsorption, distribution, metabolism, and excretion) may be a secondary objective; again, in a pharmacogenetic clinical study there may be an analysis of the effect of sequence variation in genes that affect absorption, distribution, metabolism and excretion of the candidate compound on pharmacokinetic parameters such as peak blood levels, half life or tissue distribution of the compound. As clinical development stages progress, trial objectives focus on the appropriate dose and method of administration required to elicit a clinically relevant therapeutic response. In a pharmacogenetic clinical trial, there may be a comparison of the effectiveness of several doses of a compound in patients with different genotypes, in order to identify interactions between genotype and optimal dose. For this purpose the doses selected for late stage clinical testing may be greater, equal or less than those chosen based upon preclinical safety and efficacy determinations. Data on the function of different alleles of genes affecting pharmacokinetic parameters could provide the basis for selecting an optimal dose or range or doses of a compound or biological. Genes involved in drug metabolism may be particularly useful to study in relation to understanding interpatient variation in optimal dose. Genes involved in drug metabolism include the cytochrome P450s, especially 2D6, 3A4, 2C9, 2E1, 2A6 and 1A1; the glucuronyltransferases; the acetyltransferases; the methyltransferases; the sulfotransferases; the glutathione system; the flavine monooxygenases and other enzymes known in the art.

An additional objective in the latter stages of clinical development is demonstration of the effect of the therapeutic intervention on a broad population. In phase III trials, the number of individuals enrolled is dictated by a power analysis. The number of patients required for a given pharmacogenetic clinical trial will be determined by prior knowledge of variance or haplotype frequency in the study population, likely response rate in the treated population, expected magnitude of pharmacogenetic effect (for example, the ratio of response rates between a genetic subgroup and the unfractionated population, or between two different genetic subgroups); nature of the genetic effect, if known (e.g. dominant effect, codominant effect, recessive effect); and number of genetic hypotheses to be evaluated (including number of genes and/or variances to be studied, number of gene or variance interactions to be studied). Other considerations will likely arise in the design of specific trials.

Clinical trials should be designed to blind both human subjects and study coordinators from biasing that may otherwise occur during the testing of a candidate therapeutic invention. Often the candidate therapeutic intervention is compared to best medical treatment, or a placebo (a compound, agent, device, or procedure that

appears identical to the candidate therapeutic intervention but is therapeutically inert). The combination of a placebo group and blind controls for potentially confounding factors such as prejudice on the part of study participants or investigators, insures that real, rather than perceived or expected, effects of the candidate therapeutic intervention are measured in the trials. Ideally blinding extends not only to trial subjects and investigators but also to data review committees, ancillary personnel, statisticians, and clinical trial monitors.

In pharmacogenetic clinical studies, a placebo arm or best medical control group may be required in order to ascertain the effect of the allelic variance or variances on the efficacy or toxicology of the candidate therapeutic intervention as well as placebo or best medical therapy. It will be important to assure that the composition of the control and test populations are matched, to the degree possible, with respect to genetic background and allele frequencies. This is particularly true if the variances being investigated may have an effect on disease manifestations (in addition to a hypothesized effect on response to treatment). It is likely that standard clinical trial procedures such as insuring that treatment and control groups are balanced for race, sex and age composition and other non-genetic factors relevant to disease will be sufficient to assure that genetic background is controlled, however a preferred practice is to explicitly test for genetic stratification between test and control groups. Methods for minimizing the possibility of spurious results attributable to genetic stratification between two comparison groups include the use of surrogate markers of geographic, racial and/or ethnic background, such as have been described by Rannala and coworkers. (See, for example: Rannala B, and JL Mountain. 1997 Detecting immigration by using multilocus genotypes. *Proc Natl Acad Sci U S A* Aug 19;94(17):9197-201.) One procedure would be to assure that surrogate markers of genetic background (such as those described by Rannala and Mountain) occur at comparable frequency in two comparison groups.

Open label trials are unblinded; in single blind trials patients are kept unaware of treatment assignments; in double blind trials both patients and investigators are unaware of the treatment groups; a combination of these procedures may be instituted during the trial period. Pharmacogenetic clinical trial design may include one or a combination of open label, single blind, or double blind clinical trial designs. Reduction of biases attributable to the knowledge of either the type of treatment or the genotype of the normal subjects or patients is an important aspect of study design. So, for example, even in a study that is single blind with respect to treatment, it should be possible to keep both patients and caregivers blinded to genotype during the study.

In designing a clinical trial it is important to include termination endpoints

such as adverse clinical events, inadequate study participation either in the form of lack of adherence to the clinical protocol or loss to follow up, (e.g. such that adequate power is no longer assured), lack of adherence on the part of trial investigators to the trial protocol, or lack of efficacy or positive response within the test group. In a pharmacogenetic clinical trial these considerations obtain not only in the entire treatment group, but also in the genetically defined subgroups. That is, if a dangerous toxic effect manifests itself predominantly or exclusively in a genetically defined subpopulation of the total treatment population it may be deemed inappropriate to continue treating that genetically defined subgroup. Such decisions are typically made by a data safety monitoring committee, a group of experts not including the investigators, and generally not blinded to the analysis, who review the data from an ongoing trial on a regular basis.

It is important to note that medicine is a conservative field, and clinicians are unlikely to change their behavior on the basis of a single clinical trial. Thus it is likely that, in most instances, two or more clinical trials will be required to convince physicians that they should change their prescribing habits in view of genetic information. Large scale trials represent one approach to providing increased data supporting the utility of a genetic stratification. In such trials the stringent clinical and laboratory data collection characteristic of traditional trials is often relaxed in exchange for a larger patient population. Important goals in large scale pharmacogenetic trials will include establishing whether a pharmacogenetic effect is detectable in all segments of a population. For example, in the North American population one might seek to demonstrate a pharmacogenetic effect in people of African, Asian, European and Hispanic (i.e. Mexican and Puerto Rican) origin, as well as in native American people. (It generally will not be practical to segment patients by geographical origin in a standard clinical trial, due to loss of power.) Another goal of a large scale clinical trial may be to measure more precisely, and with greater confidence, the magnitude of a pharmacogenetic effect first identified in a smaller trial. Yet another undertaking in a large scale clinical trial may be to examine the interaction of an established pharmacogenetic variable (e.g. a variance in gene A, shown to affect treatment response in a smaller trial) with other genetic variances (either in gene A or in other candidate genes). A large scale trial provides the statistical power necessary to test such interactions.

In designing all of the above stages of clinical testing investigators must be attentive to the statistical problems raised by testing multiple different hypotheses, including multiple genetic hypotheses, in subsets of patients. Bonferroni's correction or other suitable statistical methods for taking account of multiple hypothesis testing will need to be judiciously applied. However, in the early stages

of clinical testing, when the main goal is to reduce the large number of potential hypotheses that could be tested to a few that will be tested, based on limited data, it may be impractical to rigidly apply the multiple testing correction.

## B. Phase I Clinical Trials

### 1. Introduction

Phase I of clinical development is generally focused on safety, although drug companies are increasingly obtaining information on pharmacokinetics and surrogate pharmacodynamic markers in early trials. Phase I studies are typically performed with a small number (< 60) of normal, healthy volunteers usually at single institutions. The primary endpoints in these studies usually relate to pharmacokinetic parameters (i.e. adsorption, distribution, metabolism and bioavailability), and dose-related side effects. In a Phase I pharmacogenetic clinical trial, stratification based upon allelic variance or variances of a candidate gene or genes related to pharmacokinetic parameters may allow early assessment of potential genetic interactions with treatment.

Phase I studies of some diseases (e.g. cancer or other medically intractable diseases for which no effective medical alternative exists) may include patients who satisfy specified inclusion criteria. These safety/limited-efficacy studies can be conducted at multiple institutions to ensure rapid enrollment of patients. In a pharmacogenetic Phase I study that includes patients, or a mixture of patients and normals, the status of a variance or variances suspected to affect the efficacy of the candidate therapeutic intervention may be used as part of the inclusion criteria. Alternatively, analysis of variances or haplotypes in patients with different treatment responses may be among the the endpoints. It is not unusual for such a Phase I study design to include a double-blind, balanced, random-order, crossover sequence (separated by washout periods), with multiple doses on separate occasions and both pharmacokinetic and pharmacodynamic endpoints.

### 2. Phase I trials with subjects drawn from large populations and/or from related volunteer subjects: the Pharmacogenetic Phase I Unit concept

In general it is useful to be able to assess the contribution of genetic variation to treatment response at the earliest possible stage of clinical development. Such an assessment, if accurate, will allow efficient prioritization of candidate compounds for subsequent detailed pharmacogenetic studies; only those treatments where there is early evidence of a significant interaction of genetic variation with treatment response would be advanced to pharmacogenetic studies in later stages of development. In this invention we describe methods for achieving early insight – in

Phase I - into the contribution of genetic variation to variation in surrogate treatment response variables. It occurred to the inventors that this can be accomplished by bringing the power of genetic linkage analysis and outlier analysis to Phase I testing via the recruitment of a very large Phase I population including a large number of individuals who have consented in advance to genetic studies (occasionally referred to hereinafter as a Pharmacogenetic Phase I Unit). In one embodiment of a Pharmacogenetic Phase I Unit many of the subjects are related to each other by blood. (Currently Phase I trials are performed in unrelated individuals, and there is no consideration of genetic recruitment criteria, or of genetic analysis of surrogate markers.) There are several novel ways in which a large population, or a population comprised at least in part of related individuals, could be useful in early clinical trials. Some of the most attractive applications depend on the availability of surrogate markers for pharmacodynamic drug action which can be used early in clinical development, preferably in normal subjects in Phase I. Such surrogate markers are increasingly used in Phase I, as drug development companies seek to make early yes/no decisions about compounds.

Recruitment of a population optimized for clinical genetic investigation may entail utilization of methods in statistical genetics to select the size and composition of the population. For example powerful methods for detecting and mapping quantitative trait loci in sibpairs have been developed. These methods can provide some estimate of the statistical power derived from a given number of groups of closely related individuals. Ideally subjects in the pharmacogenetic Phase I unit are of known ethnic/racial/geographic background and willing to participate in Phase I studies, for pay, over a period of years. The population is preferably selected to achieve a specified degree of statistical power for genetic association studies, or is selected in order to be able to reliably identify a certain number of individuals with rare genotypes, as discussed below. Family participation could be encouraged by appropriate incentive compensation. For example, individual subjects might be paid \$200 for participation in a study; two sibs participating in the same study might each be paid \$300; if they could encourage another sib (or cousin) to participate the three related individuals might each be paid \$350, and so forth. This type of compensation would encourage subjects to recruit their relatives to participate in Phase I studies. (It would also increase the cost of studies, however the type of data that can be obtained can not be duplicated with conventional approaches.) The optimal location to establish such a Phase I unit is a city with a stable population, many large families, and a positive attitude about gene technology. The Pharmacogenetic Phase I Unit population can then be used to test for the existence of genetic variation in response to any drug as a first step in deciding whether to

proceed with extensive pharmacogenetic studies in later stages of clinical development. Specific uses of a large Phase I unit in which some or all subjects are related include:

a. It should be possible, for virtually any compound, to assess the magnitude of the genetic contribution to variation in drug response (if any) by comparing variation in drug response traits among related vs. non-related individuals. The rationale is as follows: if a surrogate drug response trait (i.e. a surrogate marker of pharmacodynamic effect that can be measured in normal subjects) is under strong genetic control then related individuals, who share 25% (cousins) or 50% (sibs) of their alleles, should have less divergent responses (less intragroup variance) than unrelated individuals, who share a much smaller fraction of alleles. That is, individuals who share alleles at the genes that affect drug response should be more similar to each other (i.e. have a narrower distribution of responses, whether measured by variance, standard deviation or other means) than individuals who, on average, share very few alleles. By using statistical methods known in the art the degree of variation in a set of data from related individuals (each individual would only be compared with his/her relatives, but such comparisons would be performed within each group of relatives and a summary statistic developed) could be compared to the degree of variation in a set of unrelated individuals (the same subjects could be used, but the second comparison would be across related groups). Account would be taken of the degree of similarity expected between related individuals, based on the fraction of the genome they shared by descent. Thus the extent of variation in the surrogate response marker between identical twins should be less than between sibs, which should be less than between first cousins, which should be less than that between second cousins, and so forth, *if* there is a genetic component to the variation. It is well known from twin studies (in which, for example, variation between identical twins is compared to variation between fraternal twins) that pharmacokinetic variables (e.g. compound half life, peak concentration) are frequently over 90% heritable; the type of study proposed here (comparison of variation within groups of sibs and cousins to variation between unrelated subjects) would also show this genetic effect, without requiring the recruitment of monozygotic twins. For a summary of pharmacokinetic studies in twins see: Propping, Paul (1978) *Pharmacogenetics. Rev. Physiol. Biochem. Pharmacol.* 83: 123-173.

It may be that the pattern of drug responses that distinguishes related individuals from non-related individuals is more complex than, for example, variance or standard deviation. For example, there may be two discrete phenotypes characteristic of intrafamilial variation (a bimodal distribution) that are not a feature

of variation between unrelated individuals (where, for example, variation might be more nearly continuous). Such a pattern could be attributable to Mendelian inheritance operating on a restricted set of alleles in a family (or families) with, for example, AA homozygotes giving one phenotype and AB heterozygotes and BB homozygotes giving a second phenotype, all in the context of a relatively homogeneous genetic background. In contrast, variation among non-related subjects would be less discrete due to a greater degree of variation in genetic background and the presence of additional alleles C, D and E at the candidate locus. Statistical measures of the significance of such differences in distribution, including nonparametric methods such as chi square and contingency tables, are known in the art.

The methods described herein for measuring whether pharmacodynamic traits are under genetic control, using surrogate markers of drug efficacy in phase I studies which include groups of related individuals, will be useful in obtaining an early assessment of the extent of genetically determined variation in drug response for a given therapeutic compound. Such information provides an informed basis for either stopping development at the earliest possible stage or, preferably, continuing with development but with a plan for identifying and controlling for genetic variation so as to allow rapid progression through the regulatory approval process.

For example, it is well known that Alzheimers trials are long and expensive, and most drugs are only effective in a fraction of patients. Using surrogate measures of response in normals drawn from a population of related individuals would help to assess the contribution of genetic variation to variation in treatment response. For an acetylcholinesterase inhibitor, relevant surrogate pharmacodynamic measures could include testing erythrocyte membrane acetylcholinesterase levels in drug treated normal subjects, or performing psychometric tests that are affected by treatment (and ideally that correlate with clinical efficacy) and measuring the effect of treatment. As another example, antidepressant drugs can produce a variety of effects on mood in normal subjects – or no effect at all. Careful monitoring and measurement of such responses in related vs. unrelated normal subjects, and statistical comparison of the degree of variation in each group, could provide an early readout on whether there is a genetic component to drug response (and hence clinical efficacy). The observation of similar effects in family members, and comparatively dissimilar effects in unrelated subjects would provide compelling evidence of a pharmacogenetic effect and justify the substantial expenditure necessary for a full pharmacogenetic drug development program. Conversely, the absence of any significant family influence on drug response would provide an early termination point for pharmacogenetic studies. *Note that the proposed studies do*

not require any knowledge of candidate genes, nor is DNA collection or genotyping required – simply a reliable surrogate pharmacodynamic assay and small groups of related normal individuals. Refined statistical methods should permit the magnitude of the pharmacogenetic effect to be measured, which could be a further criteria for deciding whether to proceed with pharmacogenetic analysis. The greater the differential in magnitude or pattern of variance between the related and the unrelated subjects, the greater the extent of genetic control of the trait.

Not all drug response traits are under the predominant control of one locus. Many such traits are under the control of multiple genes, and may be referred to as quantitative trait loci. It is then desirable to identify the major loci contributing to variation in the drug response trait. This can be done for example, to map quantitative trait loci in a population of drug treated related normals. Either a candidate gene approach or a genome wide scanning approach can be used. (For review of some relevant methods see: Hsu L, Aragaki C, Quiaoit F. (1999) A genome-wide scan for a simulated data set using two newly developed methods. *Genet Epidemiol* 17 Suppl 1:S621-6; Zhao LP, Aragaki C, Hsu L, Quiaoit F. (1998) Mapping of complex traits by single-nucleotide polymorphisms. *Am J Hum Genet* 63(1):225-40; Stoesz MR, Cohen JC, Mooser V, et al. (1997) Extension of the Haseman-Elston method to multiple alleles and multiple loci: theory and practice for candidate genes. *Ann Hum Genet* 61 (Pt 3):263-74.)) However, this method would require at least 100 patients (preferably 200, and still more preferably >300) to have adequate statistical power, and each patient would have to be genotyped at a few polymorphic loci (candidate gene approach) or hundreds of polymorphic loci (genome scanning approach).

b. With a large Phase I population of normal subjects that need not be related (a second type of Pharmacogenetic Phase I Unit) it is possible to efficiently identify and recruit for any Phase I trial a set of individuals comprising virtually any combination of genotypes present in a population (for example, all common genotypes, or a group of genotypes expected to represent outliers for a drug response trait of interest). This method preferably entails obtaining blood or other tissue (e.g. buccal smear) in advance from a large number of the subjects in the Phase I unit. Ideally consent for genotyping would be obtained at the same time. It would be most efficient if blanket consent for genotyping any polymorphic site or sites could be obtained. Second best would be consent for testing any site relevant to any customer project (not specific at the time of initial consent). Third best would be consent to genotype polymorphic sites relevant to specific disease areas. Another, less desirable, solution would be to obtain consent for genotyping on a project by



project basis (for example by mailing out reply cards), after the specific polymorphic sites to be genotyped are known.

One useful way to screen for pharmacogenetic effects in Phase I is to recruit homozygotes for a variance or variances of interest in one or more candidate genes. For example, consider a compound for which there are two genes that are strong candidates for influencing response to treatment. Gene X has alleles A and A', while gene Y has alleles B and B'. If these genes do in fact contribute significantly to response then one would expect that, regardless of the mode of inheritance (recessive, codominant, dominant, polygenic) homozygotes would exhibit the most extreme responses. One would also expect epistatic interactions, if any, to be most extreme in double homozygotes. Thus one would ideally perform a surrogate drug response test in Phase I volunteers doubly homozygous at both X and Y. That is, test AA/BB, A'A'/BB, AA/B'B' and A'A'/B'B' subjects. If the allele frequencies for A and A' are .15 and .85, and for B and B' .2 and .8 then the frequency of AA homozygotes is expected to be 2.25% and BB homozygotes 4%. In the absence of any linkage between the genes, the frequency of AA/BB double homozygotes is expected to be  $0.0225 \times 0.04 = 0.0009$  or .09%, or about 1 subject in 1000. Ideally at least 5 subjects of each genotype are recruited for the Phase I study, and preferably at least 10 subject. Thus, even for variances of moderately low allele frequency (15%, 20%), the identification of potential outliers (i.e. homozygotes) for the candidate genes of interest will require a large population. Preferably the Phase I unit has enrolled at least 1,000 normal individuals, more preferably 2,000, still more preferably 5,000 and most preferably 10,000 or more. In another application of the large, genotyped Phase I population it may be useful to identify individuals with rare variances in candidates genes (either homozygous or heterozygous), in order to determine whether those variances are predisposing to extreme pharmacological responses to the compound. For example, variances occurring at 5% allele frequency are expected to occur in homozygous form in 0.25% of the population ( $0.05 \times 0.05$ ), and therefore may rarely, if ever, be encountered in early clinical development. Yet it may be serious adverse effects occurring in just such a small group that create problems in later stages of drug development. In yet another application of the large genotyped Phase I population, subjects may be selected to represent the known common variances in one or more genes that are candidates for influencing the response to treatment. By insuring that all common genotypes are represented in a Phase I trial the likelihood of misleading results due to genetic stratification (resulting in discrepancy with results of later, larger trials can be reduced.

It would be useful to prospectively genotype the large Phase I population for variances that are commonly the source of interpatient variation in drug response, since demand for genotyped groups of such patients can be anticipated from pharmaceutical companies and contract research organizations (CROs). For example, genotyping might initially focus on common pharmacological targets such as estrogen receptors, adrenergic receptors, or serotonin receptors. The pre-genotyped Phase I population could be part of a package of services (along with genotyping assay development capability, high throughput genotyping capacity and software and expertise in statistical genetics) designed to accelerate pharmacogenetic Phase I studies. Eventually, as the databank of genotypes built up, individuals with virtually any genotype or combination of genotypes could be called in for precisely designed physiological or toxicological studies designed to test for pharmacogenetic effects.

One of the most useful aspects of the Pharmacogenetic Phase I Unit is that subjects with rare genotypes can be pharmacologically assessed in a small study. This addresses a serious limitation of conventional clinical trials with respect to the investigation of polygenic traits or the effect of rare alleles. Unfortunately even Phase III studies, as currently performed, are often barely powered to address simple one variance hypotheses about efficacy or toxicity. The problem, of course, is that each time a new genetic variable is introduced the comparison groups are cut in halves or thirds (or even smaller groups if there are multiple haplotypes at each gene). It is therefore a challenging problem to test the interaction of several genes in determining drug response. Yet the character of drug response data in populations – there is often a continuous distribution of responses among different individuals – suggests that drug responses may often be mediated by several genes. (On the other hand, there are an increasing number of well documented single gene, or even single variance, pharmacogenetic effects in the literature, showing that it is possible to detect the effect of a single variance.) One approach to identifying pharmacogenetic effects is to focus on finding the single gene variances that have the largest effects. This approach can be undertaken within the scale of current clinical trials. However, in order to develop a test which predicts a large fraction of the quantitative variation in a drug response trait it may be desirable to test the effect of multiple genes, including the interaction of variances at different genes, which may be non-additive (referred to as epistasis). The Pharmacogenetic Phase I Unit provides a way to efficiently test for gene interactions or multigene effects by, for example, allowing easy identification of individuals who, on account of being homozygous at several loci of interest, should be outliers for the drug response phenotypes of interest if there is a gene x gene interaction. Testing drug response in a small number of such

individuals will provide a quick read on gene interaction. Obtaining genetic data on the pharmacodynamic action of a compound in Phase I should also provide a crude measure of allele effects – which variances or haplotypes increase pharmacological responses and which decrease them. This information is of great value in designing subsequent trials, as it constrains the number of hypotheses to be tested, thereby enabling powerful statistical designs. This is because when the effect of variances on drug response measures is unknown one is forced to statistically test all the possible effects of each allele (e.g. two tailed tests). As the number of genetically defined groups increases (e.g. as a result of multiple variances or haplotypes) there is a loss of statistical power due to multiple testing correction. On the other hand, if the relative phenotypic effect of each allele at a locus is known (or can be hypothesized) from Phase I data then each individual in a subsequent clinical trial contributes useful information – there is a specific prediction of response based on that individuals combination of genotypes or haplotypes, and testing the fit of the actual data to those predictions provides for powerful statistical designs. (It is also possible to measure allele effects biochemically, of course, to establish which alleles have positive and which negative effects, but at considerable cost.)

It is important to note that Phase I trials can provide useful information at almost any stage of clinical development. It is not unusual, for example, for a product in Phase II or even Phase III testing to be remanded to Phase I in order to clarify some aspect of toxicology or physiology. In this context a Pharmacogenetic Phase I Unit would be extremely useful to a drug development company. Phase I studies in defined genetic subgroups drawn from a large genotyped population, or in groups of related individuals, would be the most economical and efficient way to clarify the existence of pharmacogenetic effects, if any, paving the way for future rational development of the product.

### C. Phase II Clinical Trials

Phase II studies generally include a limited number of patients (<100) who satisfy a set of predefined inclusion criteria and do not satisfy any predefined exclusion criteria of the trial protocol. Phase II studies can be conducted at single or multiple institutions. Inclusion/exclusion criteria may include historical, clinical and laboratory parameters for a disease, disorder, or condition; age; gender; reproductive status (i.e. pre- or postmenopausal); coexisting medical conditions; psychological, emotional or cognitive state, or other objective measures known to those skilled in the art. In a pharmacogenetic Phase II trial the inclusion/exclusion criteria may include one or more genotypes or haplotypes. Alternatively, genetic analysis may

be performed at the end of the trial. The primary goals in Phase II testing may include (i) identification of the optimal medical indication for the compound, (ii) definition of an optimal dose or range or doses, balancing safety and efficacy considerations (dose-finding studies), (iii) extended safety studies (complementing Phase I safety studies), (iv) evaluation of efficacy in patients with the targeted disease or condition, either in comparison to placebo or to current best therapy. To some extent these goals may be achieved by performing multiple trials with different goals. Likewise, Phase II trials may be designed specifically to evaluate pharmacogenetic aspects of the drug candidate. Primary efficacy endpoints typically focus on clinical benefit, while surrogate endpoints may measure treatment response variables such as clinical or laboratory parameters that track the progress or extent of disease, often at lesser time, cost or difficulty than the definitive endpoints. A good surrogate marker must be convincingly associated with the definitive outcome. Examples of surrogate endpoints include tumor size as a surrogate for survival in cancer trials, and cholesterol levels as a surrogate for heart disease (e.g. myocardial infarction) in trials of lipid lowering cardiovascular drugs. Secondary endpoints supplement the primary endpoint and may be selected to help guide further clinical studies.

In a pharmacogenetic Phase II clinical trial, retrospective or prospective design will include the stratification of patients based upon a variance or variances in a gene or genes suspected of affecting treatment response. The gene or genes may be involved in mediating pharmacodynamic or pharmacokinetic response to the candidate therapeutic intervention. The parameters evaluated in the genetically stratified trial population may include primary, secondary or surrogate endpoints. Pharmacokinetic parameters - for example, dosage, absorption, toxicity, metabolism, or excretion - may also be evaluated in genetically stratified groups.. Other parameters that may be assessed in parallel with genetic stratification include gender, race, ethnic or geographic origin (population history) or other demographic factors.

While it is optimal to initiate pharmacogenetic studies in phase I, as described above, it may be the case that pharmacogenetic studies are not considered until phase II, when problems relating either to efficacy or toxicity are first encountered. It is highly desirable to initiate pharmacogenetic studies no later than Phase II of a clinical development plan because (1) phase III studies tend to be large and expensive - not an optimal setting in which to explore untested pharmacogenetic hypotheses; (2) phase III studies are typically designed to test one fairly narrow hypothesis regarding efficacy of one or a few dose levels in a specific disease or condition. Phase II studies are often numerous, and are intended to

provide a broad picture of the pharmacology of the candidate compound. This is a good setting for initial pharmacogenetic studies. Several pharmacogenetic hypotheses may be tested in phase II, with the goal of eliminating all but one or two.

5     D. Phase III Clinical Trials

Phase III studies are generally designed to measure efficacy of a new treatment in comparison to placebo or to an established treatment method. Phase II studies are often performed at multiple sites. The design of this type of trial includes power analysis to ensure the sufficient data will be gathered to demonstrate the anticipated effect, making assumptions about response rate based on earlier trials. As a result Phase III trials frequently include large numbers of patients (up to 5,000). Primary endpoints in Phase III studies may include reduction or arrest of disease progression, improvement of symptoms, increased longevity or increased disease-free longevity, or other clinical measures known in the art. In a pharmacogenetic Phase III clinical study, the endpoints may include determination of efficacy or toxicity in genetically defined subgroups. Preferably the genetic analysis of outcomes will be confined to an assessment of the impact of a small number of variances or haplotypes at a small number of genes, said variances having already been statistically associated with outcomes in earlier trials. Most preferably variances at only one or two genes will be assessed.

After successful completion of one or more Phase III studies, the data and information from all trials conducted to test a new treatment method are compiled into a New Drug Application (NDA) and submitted for review by the US FDA, which has authority to grant marketing approval in the US and its territories. The NDA includes the raw (unanalyzed) clinical data, i.e. the patient by patient measurements of primary and secondary endpoints, a statistical analysis of all of the included data, a document describing in detail any observed side effects, tabulation of all patients who dropped-out of trials and detailed reasons for their termination, and any other available data pertaining to ongoing *in vitro* or *in vivo* studies since the submission of the investigational new drug (IND) application. If pharmacoeconomic objectives are a part of the clinical trial design then data supporting cost or economic analyses are included in the NDA. In a pharmacogenetic clinical study, the pharmacoeconomic analyses may include genetically stratified assessment of the candidate therapeutic intervention in a cost benefit analysis, cost of illness study, cost minimization study, or cost utility analysis. The analysis may also be simultaneously stratified by standard criteria such as race/ethnicity/geographic origin, sex, age or other criteria. Data from a genetically stratified analysis may be used to support an application for approval for

marketing of the candidate therapeutic intervention.

#### E. Phase IV Clinical Trials

Phase IV studies occur after a therapeutic intervention has been approved for  
marketing, and are typically conducted for surveillance of safety, particularly  
occurrence of rare side effects. The other principal reason for Phase IV studies is to  
produce information and relationships useful for marketing a drug. In this regard  
pharmacogenetic analysis may be very useful in Phase IV trials. Consider, for  
example, a drug that is the fourth or fifth member of a drug class (say statins, or  
thiazidinediones or fluoropyrimidines) to obtain marketing approval, and which does  
not differ significantly in clinical effects – efficacy or safety - from other members  
of the drug class. The first, second and third drugs in the class will likely have a  
dominant market position (based on their earlier introduction into the marketplace)  
that is difficult to overcome, particularly in the absence of differentiating clinical  
effects. However, it is possible that the new drug produces a superior clinical effect  
– for example, higher response rate, greater magnitude of response or fewer side  
effects - in a genetically defined subgroup. The genetic subgroup with superior  
response may constitute a larger fraction of the total patient population than the new  
drug would likely achieve otherwise. In this instance, there is a clear rationale for  
performing a Phase IV pharmacogenetic trial to identify a variance or variances that  
mark a patient population with superior clinical response. Subsequently a marketing  
campaign can be designed to alert patients, physicians, pharmacy managers,  
managed care organizations and other parties that, with the use of a rapid and  
inexpensive genetic test to identify eligible patients, the new drug is superior to  
other members of the class (including the market leading first, second and third  
drugs introduced). The high responder subgroup defined by a variance or variances  
may also exhibit a superior response to other drugs in the class (a class  
pharmacogenetic effect), or the superior efficacy in the genetic subgroup may be  
specific to the drug tested (a compound-specific pharmacogenetic effect).

In a Phase IV pharmacogenetic clinical trial, both retrospective and  
prospective analysis can be performed. In both cases, the key element is genetic  
stratification based on a variance or variances or haplotype. Phase IV trials will  
often have adequate sample size to test more than one pharmacogenetic hypothesis  
in a statistically sound way.

#### F. Unconventional Clinical Development

Although the above listed phases of clinical development are well-  
established, there are cases where strict Phase I, II, III development does not occur,

for example, in the clinical development of candidate therapeutic interventions for debilitating or life threatening diseases, or for diseases where there is presently no available treatment. Some of the mechanisms established by the FDA for such studies include Treatment INDs, Fast-Track or Accelerated reviews, and Orphan Drug Status. In a clinical development program for a candidate therapeutic of this type there is a useful role for pharmacogenetic analysis, in that the candidate therapeutic may not produce a sufficient benefit in all patients to justify FDA approval, however analysis of outcome in genetic subgroups may lead to identification of a variance or variances that predict a response rate sufficient for FDA approval.

As used herein, "supplemental applications" are those in which a candidate therapeutic intervention is tested in a human clinical trial in order to gain an expanded label indication, expanding recommended use to new medical indications. In these applications, previous clinical studies of the therapeutic intervention, i.e. preclinical safety and Phase I human safety studies can be used to support the testing of the therapeutic intervention in a new indication. Pharmacogenetic analysis is also useful in the context of clinical trials to support supplemental applications. Since these are, by definition, focused on diseases not selected for initial development the overall efficacy may not be as great as for the leading indication(s). The identification of genetic subgroups with high response rates may enable the rapid approval of supplemental applications for expanded label indications. In such instances part of the label indication may be a description of the variance or variances that define the group with superior response.

As used herein, "outcomes" or "therapeutic outcomes" describe the results and value of healthcare intervention. Outcomes can be multi-dimensional, and may include improvement of symptoms; regression of a disease, disorder, or condition; prevention of a disease or symptom; cost savings or other measures.

Pharmacoeconomics is the analysis of a therapeutic intervention in a population of patients diagnosed with a disease, disorder, or condition that includes at least one of the following studies: cost of illness study (COI); cost benefit analysis (CBA), cost minimization analysis (CMA), or cost utility analysis (CUA), or an analysis comparing the relative costs of a therapeutic intervention with one or a group of other therapeutic interventions. In each of these studies, the cost of the treatment of a disease, disorder, or condition is compared among treatment groups. Costs have both direct (therapeutic interventions, hospitalization) and indirect (loss of productivity) components. Pharmacoeconomic factors may provide the motivation for pharmacogenetic analysis, particularly for expensive therapies that benefit only a fraction of patients. For example, interferon alpha is the only

treatment that can cure hepatitis C virus infection, however viral infection is completely and permanently eliminated in less than a quarter of patients. Nearly half of patients receive virtually no benefit from alfa interferon, but may suffer significant side effects. Treatment costs are ~\$10,000 per course. A  
5 pharmacogenetic test that could predict responders would save much of the cost of treating patients not able to benefit from interferon alpha therapy, and could provide the rationale for treating a population in a cost efficient manner, where treatment would otherwise be unaffordable.

As used herein, "health-related quality of life" is a measure of the impact of a  
10 disease, disorder, or condition on a patient's activities of daily living. An analysis of the health-related quality of life is often included in pharmacoeconomic studies.

As used herein, the term "stratification" refers to the partitioning of patients into groups on the basis of clinical or laboratory characteristics of the patient.  
"Genetic stratification" refers to the partitioning of patients or normal subjects into  
15 groups based on the presence or absence of a variance or variances in one or more genes. The stratification may be performed at the end of the trial, as part of the data analysis, or may come at the beginning of a trial, resulting in creation of distinct groups for statistical or other purposes.

#### 20 *G. Power analysis in pharmacogenetic clinical trials*

The basic goal of power calculations in clinical trial design is to insure that trials have adequate patients and controls to fairly assess, with statistical significance, whether the candidate therapeutic intervention produces a clinically significant benefit.

25 Power calculations in clinical trials are related to the degree of variability of the drug response phenotypes measured and the treatment difference expected between comparison groups (e.g. between a treatment group and a control group). The smaller the variance within each group being compared, and the greater the difference in response between the two groups, the fewer patients are required to  
30 produce convincing evidence of an effect of treatment. These two factors (variance and treatment difference) determine the degree of precision required to answer a specific clinical question.

The degree of precision may be expressed in terms of the maximal acceptable standard error of a measurement, the magnitude of variation in which the  
35 95% confidence interval must be confined or the minimal magnitude of difference in a clinical or laboratory value that must be detectable (at a statistically significant level, and with a specified power for detection) in a comparison to be performed at



the end of the trial (hypothesis test). The minimal magnitude is generally set at the level that represents the minimal difference that would be considered of clinical importance.

In pharmacogenetic clinical trials there are two countervailing effects with respect to power. First, the comparison groups are reduced in size (compared to a conventional trial) due to genetic partitioning of both the treatment and control groups into two or more subgroups. However, it is reasonable to expect that variability for a trait is smaller within groups that are genetically homogeneous with respect to gene variances affecting the trait. If this is the case then power is increased as a function of the reduction in variability within (genetically defined) groups.

In general it is preferable to power a pharmacogenetic clinical trial to see an effect in the largest genetically defined subgroups. For example, for a variance with allele frequencies of 0.7 and 0.3 the common homozygote group will comprise 49% of all patients ( $0.7 \times 0.7 \times 100$ ). It is most desirable to power the trial to observe an effect (either positive or a negative) in this group. If it is desirable to measure an effect of therapy in a small genetic group (for example, the 9% of patients homozygous for the rare allele) then genotyping should be considered as an enrollment criterion to insure a sufficient number of patients are enrolled to perform an adequately powered study.

Statistical methods for powering clinical trials are known in the art. See, for example: Shuster, J.J. (1990) Handbook of Sample Size Guidelines for Clinical Trials. CRC Press, Boca Raton, FL; Machin, D. and M.J. Campbell (1987) Statistical Tables for the Design of Clinical Trials. Blackwell, Oxford, UK; Donner, A. (1984) Approaches to Sample Size Estimation in the Design of Clinical Trials – A Review. *Statistics in Medicine* 3: 199-214.

#### H. Statistical analysis of clinical trial data

There are a variety of statistical methods for measuring the difference between two or more groups in a clinical trial. One skilled in the art will recognize that different methods are suited to different data sets. In general, there is a family of methods customarily used in clinical trials, and another family of methods customarily used in genetic epidemiological studies. Methods in quantitative and population genetics designed to measure the association between genotypes and phenotypes, and to map and measure the effect of quantitative trait loci are also relevant to the task of measuring the impact of a variance on response to a treatment. Methods from any of these disciplines may be suitable for performing statistical analysis of pharmacogenetic clinical trial data, as is known to those skilled in the art.

Conventional clinical trial statistics include hypothesis testing and descriptive methods, as elaborated below. Guidance in the selection of appropriate statistical tests for a particular data set is provided in texts such as: Biostatistics: A Foundation for Analysis in the Health Sciences, 7th edition (Wiley Series in Probability and Mathematical Statistics, Applied Probability and statistics) by Wayne W. Daniel, John Wiley & Sons, 1998; Bayesian Methods and Ethics in a Clinical Trial Design (Wiley Series in Probability and Mathematical Statistics, Applied Probability Section) by J. B. Kadane (Editor), John Wiley & Sons, 1996. Examples of specific hypothesis testing and descriptive statistical procedures that may be useful in analyzing clinical trial data are listed below.

A. Hypothesis testing statistical procedures

(1) One-sample procedures (binomial confidence interval, Wilcoxon signed rank test, permutation test with general scores, generation of exact permutational distributions)

(2) Two-sample procedures (*t*-test, Wilcoxon-Mann-Whitney test, Normal score test, Median test, Van der Waerden test, Savage test, Logrank test for censored survival data, Wilcoxon-Gehan test for censored survival data, Cochran-Armitage trend test, permutation test with general scores, generation of exact permutational distributions)

(3) R x C contingency tables (Fisher's exact test, Pearson's chi-squared test, Likelihood ratio test, Kruskal-Wallis test, Jonckheere-Terpstra test, Linear-by-linear association test, McNemar's test, marginal homogeneity test for matched pairs)

(4) Stratified 2 x 2 contingency tables (test of homogeneity for odds ratio, test of unity for the common odds ratio, confidence interval for the common odds ratio)

(5) Stratified 2 x C contingency tables (all two-sample procedures listed above with stratification, confidence intervals for the odds ratios and trend, generation of exact permutational distributions)

(6) General linear models (simple regression, multiple regression, analysis of variance -ANOVA-, analysis of covariance, response-surface models, weighted regression, polynomial regression, partial correlation, multiple analysis of variance -MANOVA-, repeated measures analysis of variance).

(7) Analysis of variance and covariance with a nested (hierarchical) structure.

(8) Designs and randomized plans for nested and crossed experiments (completely randomized design for two treatment, split-plot design, hierarchical design, incomplete block design, latin square design)

(9) Nonlinear regression models

(10) Logistic regression for unstratified or stratified data, for binary or ordinal response data, using the logit link function, the normit function or the complementary log-log function.

(11) Probit, logit, ordinal logistic and gompit regression models.

(12) Fitting parametric models to failure time data that may be right-, left-, or interval-censored. Tested distributions can include extreme value, normal and logistic distributions, and, by using a log transformation, exponential, Weibull, lognormal, loglogistic and gamma distributions.

(13) Compute non-parametric estimates of survival distribution with right-censored data and compute rank tests for association of the response variable with other variables.

#### B. Descriptive statistical methods

- Factor analysis with rotations
- Canonical correlation
- Principal component analysis for quantitative variables.
- Principal component analysis for qualitative data.
- Hierarchical and dynamic clustering methods to create tree structure, dendrogram or phenogram.
- Simple and multiple correspondence analysis using a contingency table as input or raw categorical data.

Specific instructions and computer programs for performing the above calculations can be obtained from companies such as: SAS/STAT Software, SAS Institute Inc., Cary, NC, USA; BMDP Statistical Software, BMDP Statistical Software Inc., Los Angeles, CA, USA; SYSTAT software, SPSS Inc., Chicago, IL, USA; StatXact & LogXact, CYTEL Software Corporation, Cambridge, MA, USA.

#### C. Statistical Genetic Methods Useful for Analysis of Pharmacogenetic Data

A wide spectrum of mathematical and statistical tools may be useful in the analysis of data produced in pharmacogenetic clinical trials, including methods employed in molecular, population, and quantitative genetics, as well as genetic epidemiology. Methods developed for plant and animal breeding may be useful as well, particularly methods relating to the genetic analysis of quantitative traits.

Analytical methods useful in the analysis of genetic variation among individuals, populations and species of various organisms are described in the following texts: Molecular Evolution, by W- H. Li, Sinauer Associates, Inc., 1997; Principles of Population Genetics, by D. L. Hartl and A. G. Clark, 1996; Genetics and Analysis of Quantitative Traits, By M. Lynch and B. Walsh, Sinauer Associates, Inc., Principles of Quantitative Genetics, by D. S. Falconer and T.F.C. Mackay, Longman, 1996; Genetic Variation and Human Disease, by K. M. Weiss, Cambridge University Press, 1993; Fundamentals of Genetic Epidemiology, by M. J. Khoury, T. H. Beaty, and B. H. Cohen, Oxford University Press, 1993; Handbook of Genetic Linkage, by J. Terwilliger J. Ott, Johns Hopkins University Press, 1994.

The types of statistical analysis performed in different branches of genetics are outlined below as a guide to the relevant literature and publicly available software, some of which is cited.

#### *Molecular evolutionary genetics*

- Patterns of nucleotide variation among individuals, families/populations and across species and genera,
- Alignment of sequences and description of variation/polymorphisms among the aligned sequences, amounts of similarities and dissimilarities,
- Measurement of molecular variation among various regions of a gene, testing of neutrality models,
- Rates of nucleotide changes among coding and the non-coding regions within and among populations,
- Construction of phylogenetic trees using methods such as neighborhood joining and maximum parsimony; estimation of ages of variances using coalescent models,

#### *Population genetics*

- Patterns of distribution of genes among genotypes and populations. Hardy-Weinberg equilibrium, departures from the equilibrium
- Genotype and haplotype frequencies, levels of heterozygosities, polymorphism information contents of genes, estimation of haplotypes from genotypes; the E-M algorithm, and parsimony methods
- Estimation of linkage disequilibrium and recombination
- Hierarchical structure of populations, the F-statistics, estimation of inbreeding, selection and drift
- Genetic admixture/migration and mutation frequencies
- Spatial distribution of genotypes using spatial autocorrelation methods
- Kin-structured maintenance of variation and migration

#### *Quantitative genetics*

- Phenotype as the product of the interaction between genotype and environment
- Additive, dominance and epistatic variance on the phenotype
- Effects of homozygosity, heterozygosity and developmental homeostasis
- Estimation of heritability: broad sense and narrow sense

- Determination of number of genes governing a character
- Determination of quantitative trait loci (QTLs) using family information or population information, and using linkage and/or association studies
- Determination of quantitative trait nucleotide (QTN) using a combination  
linkage disequilibrium methods and cladistic approaches
- Determination of individual causal nucleotide in the diploid or haploid state on the phenotype using the method of measured genotype approaches, and combined effects or synergistic interaction of the causal mutations on the phenotype
- Determination of relative importance of each of the mutations on a given phenotype using multivariate methods, such as discriminant function, principal component and step-wise regression methods
- Determination of direct and indirect effect of polymorphisms on a complex phenotype using path analysis (partial regression ) methods
- Determination of the effects of specific environment on a given genotype – genotype x environment interactions using joint regression and additive and multiplicative parameter methods.

#### *Genetic epidemiology*

- Determination of sample size based on the disease and the marker frequency in the “case” and in the “control” populations
- Stratification of study population based on gender, ethnic, socio-economic variation
- Establishing a “causal relationship” between genotype and disease, using , using various association and linkage approaches – viz., case-control designs, family studies (if available), transmission disequilibrium tests etc.,
- Linkage analysis between markers and a candidate locus using two-point and multipoint approaches.

Computer programs used for genetic analysis are: Dna SP version 3.0, by Juilo Rozas, University of Barcelona, Spain. <http://www.bio.ub.es/~Julio>; Arlequin 1.1 by S. Schnieder, J-M Kueffer, D. Roessli and L. Excoffier. University of Geneva, Switzerland, <http://anthropologie.unige.ch/arlequin>. PAUP\*4, by D. L. Swofford, Sinauer Associates, Inc., 1999. SYSTAT software, SPSS Inc., Chicago, Il., 1998; . Linkage User’s Guide, by J. Ott, Rockefeller University, <http://Linkage.rockefeller.edu/soft/linkage>

Guidance in the selection of appropriate genetic statistical tests for analysis of data can be obtained from texts such as: Fundamentals of Genetic Epidemiology (Monographs in Epidemiology and Biostatistics, Vol 22) by M. J. Khoury, B. H. Cohen & T. H. Beaty, Oxford Univ Press, 1993; Methods in Genetic Epidemiology by Newton E. Morton, S. Karger Publishing, 1983; Methods in Observational Epidemiology, 2nd edition (Monographs in Epidemiology and Biostatistics, V. 26) by J. L. Kelsey (Editor), A. S. Whittemore & A. S. Evans, 1996; Clinical Trials : Design, Conduct, and Analysis (Monographs in Epidemiology and Biostatistics, Vol 8) by C. L. Meinert & S. Tonascia, 1986)

I. Retrospective clinical trials.

In general the goal of retrospective clinical trials is to test and refine hypotheses regarding genetic factors that are associated with drug responses. The best supported hypotheses can subsequently be tested in prospective clinical trials, and data from the prospective trials will likely comprise the main basis for an application to register the drug and predictive genetic test with the appropriate regulatory body. In some cases, however, it may become acceptable to use data from retrospective trials to support regulatory filings. Exemplary strategies and criteria for stratifying patients in a retrospective clinical trial are provided below.

Clinical trials to study the effect of one gene locus on drug response

A. Stratify patients by genotype at one candidate variance in the candidate gene locus.

1. Genetic stratification of patients can be accomplished in several ways, including the following (where 'A' is the more frequent form of the variance being assessed and 'a' is the less frequent form):

(a) AA vs. aa

(b) AA vs. Aa vs. aa

(c) AA vs. (Aa + aa)

(d) (AA + Aa) vs. aa.

2. The effect of genotype on drug response phenotype may be affected by a variety of nongenetic factors. Therefore it may be beneficial to measure the effect of genetic stratification in a subgroup of the overall clinical trial population.

Subgroups can be defined in a number of ways including, for example, biological, clinical, pathological or environmental criteria. For example, the predictive value of genetic stratification can be assessed in a subgroup or subgroups defined by:

a. Biological criteria:

i. gender (males vs. females)

ii. age (for example above 60 years of age). Two, three or more age groups may be useful for defining subgroups for the genetic analysis.

iii. hormonal status and reproductive history, including pre- vs. post-menopausal status of women, or multiparous vs. nulliparous women

iv. ethnic, racial or geographic origin, or surrogate markers of ethnic, racial or geographic origin. (For a description of genetic markers that serve as surrogates of racial/thnic origin see, for example: Rannala, B. and J.L. Mountain, Detecting immigration by using multilocus genotypes. *Proc Natl Acad Sci U S A*, 94 (17):

9197-9201, 1997. Other surrogate markers could be used, including biochemical markers.)

b. Clinical criteria:

i. Disease status. There are clinical grading scales for many diseases. For example, the status of Alzheimer's Disease patients is often measured by cognitive assessment scales such as the mini-mental status exam (MMSE) or the Alzheimer's Disease Assessment Scale (ADAS), which includes a cognitive component (ADAS-COG). There are also clinical assessment scales for many other diseases, including cancer.

ii. Disease manifestations (clinical presentation).

iii. Radiological staging criteria.

c. Pathological criteria:

i. Histopathologic features of disease tissue, or pathological diagnosis. (For example there are many varieties of lung cancer: squamous cell carcinoma, adenocarcinoma, small cell carcinoma, bronchoalveolar carcinoma, etc., each of which may – which, in combination with genetic variation, may correlate with

ii. Pathological stage. A variety of diseases, particularly cancer, have pathological staging schemes

iii. Loss of heterozygosity (LOH)

iv. Pathology studies such as measuring levels of a marker protein

v. Laboratory studies such as hormone levels, protein levels, small molecule levels

3. Measure frequency of responders in each genetic subgroup. Subgroups may be defined in several ways.

i. more than two age groups

ii. reproductive status such as pre or post-menopausal

4. Stratify by haplotype at one candidate locus where the haplotype is made up of two variances, three variances or greater than three variances.

Data from already completed clinical trials can be retrospectively reanalyzed. Since the questions are new, the data can be treated as if it were a prospective trial, with identified variances or haplotypes as stratification criteria or endpoints in clinically stratified data (e.g. what is the frequency of a particular variance in a response group compared to nonresponders). Care should be taken to in studying a population in which there may be a link between drug-related genes and disease-related genes.

Retrospective pharmacogenetic trials can be conducted at each of the phases

of clinical development, if sufficient data is available to correlate the physiologic effect of the candidate therapeutic intervention and the allelic variance or variances within the treatment population. In the case of a retrospective trial, the data collected from the trial can be re-analyzed by imposing the additional stratification on groups of patients by specific allelic variances that may exist in the treatment groups. Retrospective trials can be useful to ascertain whether a hypothesis that a specific variance has a significant effect on the efficacy or toxicity profile for a candidate therapeutic intervention.

A prospective clinical trial has the advantage that the trial can be designed to ensure the trial objectives can be met with statistical certainty. In these cases, power analysis, which includes the parameters of allelic variance frequency, number of treatment groups, and ability to detect positive outcomes can ensure that the trial objectives are met.

In designing a pharmacogenetic trial, retrospective analysis of Phase II or Phase III clinical data can indicate trial variables for which further analysis is beneficial. For example, surrogate endpoints, pharmacokinetic parameters, dosage, efficacy endpoints, ethnic and gender differences, and toxicological parameters may result in data that would require further analysis and re-examination through the design of an additional trial. In these cases, analysis involving statistics, genetics, clinical outcomes, and economic parameters may be considered prior to proceeding to the stage of designing any additional trials. Factors involved in the consideration of statistical significance may include Bonferroni analysis, permutation testing, with multiple testing correction resulting in a difference among the treatment groups that has occurred as a result of a chance of no greater than 20%, i.e.  $p < 0.20$ . Factors included in determining clinical outcomes to be relevant for additional testing may include, for example, consideration of the target indication, the trial endpoints, progression of the disease, disorder, or condition during the trial study period, biochemical or pathophysiologic relevance of the candidate therapeutic intervention, and other variables that were not included or anticipated in the initial study design or clinical protocol. Factors to be included in the economic significance in determining additional testing parameters include sample size, accrual rate, number of clinical sites or institutions required, additional or other available medical or therapeutic interventions approved for human use, and additional or other available medical or therapeutic interventions concurrently or anticipated to enter human clinical testing. Further, there may be patients within the treatment categories that present data that fall outside of the average or mean values, or there may be an indication of multiple allelic loci that are involved in the responses to the candidate therapeutic intervention. In these cases, one could propose a prospective clinical trial having an



objective to determine the significance of the variable or parameter and its effect on the outcome of the parent Phase II trial. In the case of a pharmacogenetic difference, i.e. a single or multiple allelic difference, a population could be selected based upon the distribution of genotypes. The candidate therapeutic intervention could then be tested in this group of volunteers to test for efficacy or toxicity. The repeat prospective study could be a Phase I limited study in which the subjects would be healthy human volunteers, or a Phase II limited efficacy study in which patients which satisfy the inclusion criteria could be enrolled. In either case, the second, confirmatory trial could then be used to systematically ensure an adequate number of patients with appropriate phenotype is enrolled in a Phase III trial.

A placebo controlled pharmacogenetics clinical trial design will be one in which target allelic variance or variances will be identified and a diagnostic test will be performed to stratify the patients based upon presence, absence, or combination thereof of these variances. In the Phase II or Phase III stage of clinical development, determination of a specific sample size of a prospective trial will be described to include factors such as expected differences between a placebo and treatment on the primary or secondary endpoints and a consideration of the allelic frequencies.

The design of a pharmacogenetics clinical trial will include a description of the allelic variance impact on the observed efficacy between the treatment groups. Using this type of design, the type of genetic and phenotypic relationship display of the efficacy response to a candidate therapeutic intervention will be analyzed. For example, a genotypically dominant allelic variance or variances will be those in which both heterozygotes and homozygotes will demonstrate a specific phenotypic efficacy response different from the homozygous recessive genotypic group. A pharmacogenetic approach is useful for clinicians and public health professionals to include or eliminate small groups of responders or non-responders from treatment in order to avoid unjustified side-effects. Further, adjustment of dosages when clear clinical difference between heterozygous and homozygous individuals may be beneficial for therapy with the candidate therapeutic intervention

In another example, a recessive allelic variance or variances will be those in which only the homozygote recessive for that or those variances will demonstrate a specific phenotypic efficacy response different from the heterozygotes or homozygous dominants. An extension of these examples may include allelic variance or variances organized by haplotypes from additional gene or genes.

## **V. Variance Identification and Use**

### **A. Initial Identification of variances in genes**

*Selection of population size and composition*

Prior to testing to identify the presence of sequence variances in a particular gene or genes, it is useful to understand how many individuals should be screened to provide confidence that most or nearly all pharmacogenetically relevant variances will be found. The answer depends on the frequencies of the phenotypes of interest and what assumptions we make about heterogeneity and magnitude of genetic effects. Prior to testing to identify the presence of sequence variances in a particular gene or genes, it is useful to understand how many individuals should be screened to provide confidence that most or nearly all pharmacogenetically relevant variances will be found. The answer depends on the frequencies of the phenotypes of interest and what assumptions we make about heterogeneity and magnitude of genetic effects. At the beginning we only know phenotype frequencies (e.g. responders vs. nonresponders, frequency of various side effects, etc.).

The most conservative assumption (resulting in the lowest estimate of allele frequency, and consequently the largest suggested screening population) is (i) that the phenotype (e.g. toxicity or efficacy) is multifactorial (i.e. can be caused by two or more variances or combinations of variances), (ii) that the variance of interest has a high degree of penetrance (i.e. is consistently associated with the phenotype), and (iii) that the mode of transmission is Mendelian dominant. Consider a pharmacogenetic study designed to identify predictors of efficacy for a compound that produces a 15% response rate in a nonstratified population. If half the response is substantially attributable to a given variance, and the variance is consistently associated with a positive response (in 80% of cases) and the variance need only be present in one copy to produce a positive result then ~10% of the subjects are likely heterozygotes for the variance that produces the response. The Hardy-Weinberg equation can be used to infer an allele frequency in the range of 5% from these assumptions (given allele frequencies of 5%/95% then:  $2 \times .05 \times .95 = .095$ , or 9.5% heterozygotes are expected, and  $0.05 \times 0.05 = 0.0025$ , or 0.25% homozygotes are expected. They sum to  $9.5\% + 0.25\% = 9.75\%$  likely responders, 80% of whom, or 7.6%, are likely real responders due to presence of the positive response allele. Thus about half of the 15% responders are accounted for.). From the Table it can be seen that, in order to have a 99% chance of detecting an allele present at a frequency of 5% nearly 50 subjects should be screened for variances, assuming that the variances occur in the screening population at the same frequency as they occur in the patient population. Similar analyses can be performed for other assumptions regarding likely magnitude of effect, penetrance and mode of genetic transmission.

At the beginning we only know phenotype frequencies (e.g. responders vs. nonresponders, frequency of various side effects, etc.). As an example, the occurrence of serious 5-FU/FA toxicity - e.g. toxicity requiring hospitalization is often >10%. The occurrence of life threatening toxicity is in the 1-3% range (Buroker et al. 1994). The occurrence of complete remissions is on the order of 2-8%. The lowest frequency phenotypes are thus on the order of ~2%. If we assume that (i) homogeneous genetic effects are responsible for half the phenotypes of interest and (ii) for the most part the extreme phenotypes represent recessive genotypes, then we need to detect alleles that will be present at ~10% frequency ( $.1 \times .1 = .01$ , or 1% frequency of homozygotes) if the population is at Hardy-Weinberg equilibrium. To have a ~99% chance of identifying such alleles would require searching a population of 22 individuals (see Table below). If the major phenotypes are associated with heterozygous genotypes then we need to detect alleles present at ~.5% frequency ( $2 \times .005 \times .995 = .00995$ , or ~1% frequency of heterozygotes). A 99% chance of detecting such alleles would require ~40 individuals (Table below). Given the heterogeneity of the North American population we cannot assume that all genotypes are present in Hardy-Weinberg proportions, therefore a substantial oversampling may be done to increase the chances of detecting relevant variances: For our initial screening, usually, 62 individuals of known race/ethnicity are screened for variance. Variance detection studies can be extended to outliers for the phenotypes of interest to cover the possibility that important variances were missed in the normal population screening.

| Allele frequencies | Number of subjects genotyped |        |        |        |        |        |        |        |
|--------------------|------------------------------|--------|--------|--------|--------|--------|--------|--------|
|                    | n = 5                        | n = 10 | n = 15 | n = 20 | n = 25 | n = 30 | n = 35 | n = 50 |
| p=.99,             | 9.56                         | 18.21  | 26.03  | 33.10  | 39.50  | 45.28  | 50.52  | 63.40  |
| p=.97,             | 26.26                        | 45.62  | 59.90  | 70.43  | 78.19  | 83.92  | 88.14  | 95.24  |
| p=.95,             | 40.13                        | 64.15  | 78.53  | 87.15  | 92.30  | 95.39  | 97.24  | 99.65  |
| p=.93,             | 51.60                        | 76.58  | 88.66  | 94.51  | 97.34  | 98.71  | 99.38  | 99.93  |
| p=.9, q =          | 65.13                        | 87.84  | 95.76  | 98.52  | 99.48  | 99.82  | 99.94  | >99.9  |
| p=.8, q =          | 89.26                        | 98.84  | 99.88  | 99.99  | >99.9  | >99.9  | >99.9  | >99.9  |
| p=.7, q =          | 97.17                        | 99.92  | 99.99  | >99.9  | >99.9  | >99.9  | >99.9  | >99.9  |

*Likelihood of Detecting Polymorphism in a Population as a Function of Allele Frequency & Number of Individuals Genotyped*

The table above shows the probability (expressed as percent) of detecting both alleles (i.e. detecting heterozygotes) at a biallelic locus as a function of (i) the allele frequencies and (ii) the number of individuals genotyped. The chances of detecting heterozygotes increases as the frequencies of the two alleles approach 0.5 (down a column), and as the number of individuals genotyped increases (to the right along a row). The numbers in the table are given by the formula:  $1 - (p)^{2n} - (q)^{2n}$ . Allele frequencies are designated p and q and the number of individuals tested is designated n. (Since humans are diploid, the number of alleles tested is twice the number of individuals, or 2n.)

While it is preferable that numbers of individuals, or independent sequence samples, are screened to identify variances in a gene, it is also very beneficial to identify variances using smaller numbers of individuals or sequence samples. For example, even a comparison between the sequences of two samples or individuals can reveal sequence variances between them. Preferably, 5, 10, or more samples or individuals are screened.

#### *Source of nucleic acid samples*

Nucleic acid samples, for example for use in variance identification, can be obtained from a variety of sources as known to those skilled in the art, or can be obtained from genomic or cDNA sources by known methods. For example, the Coriell Cell Repository (Camden, N.J.) maintains over 6,000 human cell cultures, mostly fibroblast and lymphoblast cell lines comprising the NIGMS Human Genetic Mutant Cell Repository. A catalog (<http://locus.umdj.edu/nigms>) provides racial or ethnic identifiers for many of the cell lines. It is preferable to perform polymorphism discovery on a population that mimics the population to be evaluated in a clinical trial, both in terms of racial/ethnic/geographic background and in terms of disease status. Otherwise, it is generally preferable to include a broad population sample including, for example, (for trials in the United States): Caucasians of Northern, Central and Southern European origin, Africans or African-Americans, Hispanics or Mexicans, Chinese, Japanese, American Indian, East Indian, Arabs and Koreans.

#### *Source of human DNA, RNA and cDNA samples*

PCR based screening for DNA polymorphism can be carried out using either genomic DNA or cDNA produced from mRNA. For many genes, only cDNA sequences have been published, therefore the analysis of those genes is, at least initially, at the cDNA level since the determination of intron-exon boundaries and the isolation of flanking sequences is a laborious process. However, screening

genomic DNA has the advantage that variances can be identified in promoter, intron and flanking regions. Such variances may be biologically relevant. Therefore preferably, when variance analysis of patients with outlier responses is performed, analysis of selected loci at the genomic level is also performed. Such analysis would be contingent on the availability of a genomic sequence or intron-exon boundary sequences, and would also depend on the anticipated biological importance of the gene in connection with the particular response.

When cDNA is to be analyzed it is very beneficial to establish a tissue source in which the genes of interest are expressed at sufficient levels that cDNA can be readily produced by RT-PCR. Preliminary PCR optimization efforts for 19 of the 29 genes in Table 2 reveal that all 19 can be amplified from lymphoblastoid cell mRNA. The 7 untested genes belong on the same pathways and are expected to also be PCR amplifiable.

#### *PCR Optimization*

Primers for amplifying a particular sequence can be designed by methods known to those skilled in the art, including by the use of computer programs such as the PRIMER software available from Whitehead Institute/MIT Genome Center. In some cases it is preferable to optimize the amplification process according to parameters and methods known to those skilled in the art; optimization of PCR reactions based on a limited array of temperature, buffer and primer concentration conditions is utilized. New primers are obtained if optimization fails with a particular primer set.

#### *Variance detection using T4 endonuclease VII mismatch cleavage method*

Any of a variety of different methods for detecting variances in a particular gene can be utilized, such as those described in the patents and applications cited in section A above. An exemplary method is a T4 EndoVII method. The enzyme T4 endonuclease VII (T4E7) is derived from the bacteriophage T4. T4E7 specifically cleaves heteroduplex DNA containing single base mismatches, deletions or insertions. The site of cleavage is 1 to 6 nucleotides 3' of the mismatch. This activity has been exploited to develop a general method for detecting DNA sequence variances (Youil et al. 1995; Mashal and Sklar, 1995). A quality controlled T4E7 variance detection procedure based on the T4E7 patent of R.G.H. Cotton and co-workers. (Del Tito et al., in press) is preferably utilized. T4E7 has the advantages of being rapid, inexpensive, sensitive and selective. Further, since the enzyme

pinpoints the site of sequence variation, sequencing effort can be confined to a 25 - 30 nucleotide segment.

The major steps in identifying sequence variations in candidate genes using T4E7 are: (1) PCR amplify 400-600 bp segments from a panel of DNA samples; (2) mix a fluorescently-labeled probe DNA with the sample DNA; (3) heat and cool the samples to allow the formation of heteroduplexes; (4) add T4E7 enzyme to the samples and incubate for 30 minutes at 37°C, during which cleavage occurs at sequence variance mismatches; (5) run the samples on an ABI 377 sequencing apparatus to identify cleavage bands, which indicate the presence and location of variances in the sequence; (6) a subset of PCR fragments showing cleavage are sequenced to identify the exact location and identity of each variance.

The T4E7 Variance Imaging procedure has been used to screen particular genes. The efficiency of the T4E7 enzyme to recognize and cleave at all mismatches has been tested and reported in the literature. One group reported detection of 81 of 81 known mutations (Youil et al. 1995) while another group reported detection of 16 of 17 known mutations (Mashal and Sklar, 1995). Thus, the T4E7 method provides highly efficient variance detection.

#### *DNA sequencing*

A subset of the samples containing each unique T4E7 cleavage site is selected for sequencing. DNA sequencing can, for example, be performed on ABI 377 automated DNA sequencers using BigDye chemistry and cycle sequencing. Analysis of the sequencing runs will be limited to the 30-40 bases pinpointed by the T4E7 procedure as containing the variance. This provides the rapid identification of the altered base or bases.

In some cases, the presence of variances can be inferred from published articles which describe Restriction Fragment Length Polymorphisms (RFLP). The sequence variances or polymorphisms creating those RFLPs can be readily determined using convention techniques, for example in the following manner. If the RFLP was initially discovered by the hybridization of a cDNA, then the molecular sequence of the RFLP can be determined by restricting the cDNA probe into fragments and separately hybridizing to a Southern blot consisting of the restriction digestion with the enzyme which reveals the polymorphic site, identifying the sub-fragment which hybridizes to the polymorphic restriction fragment, obtaining a genomic clone of the gene (e.g., from commercial services such as Genome Systems (Saint Louis, Missouri) or Research Genetics (Alabama) which will provide appropriate genomic clones on receipt of appropriate primer pairs). Using the genomic clone, restrict the genomic clone with the restriction enzyme

which revealed the polymorphism and isolate the fragment which contains the polymorphism, e.g., identifying by hybridization to the cDNA which detected the polymorphism. The fragment is then sequenced across the polymorphic site. A copy of the other allele can be obtained by PCT from addition samples.

5     *Variance detection using sequence scanning*

In addition to the physical methods, e.g., those described above and others known to those skilled in the art (see, e.g., Housman, U.S. Patent 5,702,890; Housman et al., U.S. Patent Application 09/045,053), variances can be detected using computational methods, involving computer comparison of sequences from  
10     two or more different biological sources, which can be obtained in various ways, for example from public sequence databases. The term "variance scanning" refers to a process of identifying sequence variances using computer-based comparison and analysis of multiple representations of at least a portion of one or more genes. Computational variance detection involves a process to distinguish true variances  
15     from sequencing errors or other artifacts, and thus does not require perfectly accurate sequences. Such scanning can be performed in a variety of ways, preferably, for example, as described in Stanton et al., filed October 14, 1999, serial number 09/419,705, attorney docket number 246/128.

While the utilization of complete cDNA sequences is highly preferred, it is  
20     also possible to utilize genomic sequences. Such analysis may be desired where the detection of variances in or near splice sites is sought. Such sequences may represent full or partial genomic DNA sequences for a gene or genes. Also, as previously indicated, partial cDNA sequences can also be utilized although this is less preferred. As described below, the variance scanning analysis can simply  
25     utilize sequence overlap regions, even from partial sequences. Also, while the present description is provided by reference to DNA, e.g., cDNA, some sequences may be provided as RNA sequences, e.g., mRNA sequences. Such RNA sequences may be converted to the corresponding DNA sequences, or the analysis may use the RNA sequences directly.

30     B.     Determination of Presence or Absence of Known Variances

The identification of the presence of previously identified variances in cells of an individual, usually a particular patient, can be performed by a number of different techniques as indicated in the Summary above. Such methods include  
35     methods utilizing a probe which specifically recognizes the presence of a particular nucleic acid or amino acid sequence in a sample. Common types of probes include nucleic acid hybridization probes and antibodies, for example, monoclonal

antibodies, which can differentially bind to nucleic acid sequences differing in one or more variance sites or to polypeptides which differ in one or more amino acid residues as a result of the nucleic acid sequence variance or variances. Generation and use of such probes is well-known in the art and so is not described in detail  
5 herein.

Preferably, however, the presence or absence of a variance is determined using nucleotide sequencing of a short sequence spanning a previously identified variance site. This will utilize validated genotyping assays for the polymorphisms previously identified. Since both normal and tumor cell genotypes can be measured,  
10 and since tumor material will frequently only be available as paraffin embedded sections (from which RNA cannot be isolated), it will be necessary to utilize genotyping assays that will work on genomic DNA. Thus PCR reactions will be designed, optimized, and validated to accommodate the intron-exon structure of each of the genes. If the gene structure has been published (as it has for some of the  
15 listed genes), PCR primers can be designed directly. However, if the gene structure is unknown, the PCR primers may need to be moved around in order to both span the variance and avoid exon-intron boundaries. In some cases one-sided PCR methods such as bubble PCR (Ausubel et al. 1997) may be useful to obtain flanking intronic DNA for sequence analysis.

20 Using such amplification procedures, the standard method used to genotype normal and tumor tissues will be DNA sequencing. PCR fragments encompassing the variances will be cycle sequenced on ABI 377 automated sequencers using Big Dye chemistry

#### 25 C. Correlation of the Presence or Absence of Specific Variances with Differential Treatment Response

Prior to establishment of a diagnostic test for use in the selection of a treatment method or elimination of a treatment method, the presence or absence of one or more specific variances in a gene or in multiple genes is correlated with a  
30 differential treatment response. (As discussed above, usually the existence of a variable response and the correlation of such a response to a particular gene is performed first.) Such a differential response can be determined using prospective and/or retrospective data. Thus, in some cases, published reports will indicate that the course of treatment will vary depending on the presence or absence of particular  
35 variances. That information can be utilized to create a diagnostic test and/or incorporated in a treatment method as an efficacy or safety determination step.

Usually, however, the effect of one or more variances is separately determined. The determination can be performed by analyzing the presence or



absence of particular variances in patients who have previously been treated with a particular treatment method, and correlating the variance presence or absence with the observed course, outcome, and/or development of adverse events in those patients. This approach is useful in cases in which observation of treatment effects was clearly recorded and cell samples are available or can be obtained.

Alternatively, the analysis can be performed prospectively, where the presence or absence of the variance or variances in an individual is determined and the course, outcome, and/or development of adverse events in those patients is subsequently or concurrently observed and then correlated with the variance determination.

#### *Analysis of Haplotypes Increases Power of Genetic Analysis*

In some cases, variation in activity due to a single gene or a single genetic variance in a single gene may not be sufficient to account for a clinically significant fraction of the observed variation in patient response to a treatment, e.g., a drug, there may be other factors that account for some of the variation in patient response. Drug response phenotypes may vary continuously, and such (quantitative) traits may be influenced by a number of genes (Falconer and Mackay, Quantitative Genetics, 1997). Although it is impossible to determine *a priori* the number of genes influencing a quantitative trait, potentially only one or a few loci have large effects, where a large effect is 5-20% of total variation in the phenotype (Mackay, 1995).

Having identified genetic variation in enzymes that may affect action of a specific drug, it is useful to efficiently address its relation to phenotypic variation. The sequential testing for correlation between phenotypes of interest and single nucleotide polymorphisms may be adequate to detect associations if there are major effects associated with single nucleotide changes; certainly it is useful to this type of analysis. However there is no way to know in advance whether there are major phenotypic effects associated with single nucleotide changes and, even if there are, there is no way to be sure that the salient variance has been identified by screening cDNAs. A more powerful way to address the question of genotype-phenotype correlation is to assort genotypes into haplotypes. (A haplotype is the *cis* arrangement of polymorphic nucleotides on a particular chromosome.) Haplotype analysis has several advantages compared to the serial analysis of individual polymorphisms at a locus with multiple polymorphic sites.

(1) Of all the possible haplotypes at a locus ( $2^n$  haplotypes are theoretically possible at a locus with  $n$  binary polymorphic sites) only a small fraction will

generally occur at a significant frequency in human populations. Thus, association studies of haplotypes and phenotypes will involve testing fewer hypotheses. As a result there is a smaller probability of Type I errors, that is, false inferences that a particular variant is associated with a given phenotype.

(2) The biological effect of each variance at a locus may be different both in magnitude and direction. For example, a polymorphism in the 5' UTR may affect translational efficiency, a coding sequence polymorphism may affect protein activity, a polymorphism in the 3' UTR may affect mRNA folding and half life, and so on. Further, there may be interactions between variances: two neighboring polymorphic amino acids in the same domain - say cys/arg at residue 29 and met/val at residue 166 - may, when combined in one sequence, for example, 29cys-166val, have a deleterious effect, whereas 29cys-166met, 29arg-166met and 29arg-166val proteins may be nearly equal in activity. Haplotype analysis is the best method for assessing the interaction of variances at a locus.

(3) Templeton and colleagues have developed powerful methods for assorting haplotypes and analyzing haplotype/phenotype associations (Templeton et al., 1987). Alleles which share common ancestry are arranged into a tree structure (cladogram) according to their (inferred) time of origin in a population (that is, according to the principle of parsimony). Haplotypes that are evolutionarily ancient will be at the center of the branching structure and new ones (reflecting recent mutations) will be represented at the periphery, with the links representing intermediate steps in evolution. The cladogram defines which haplotype-phenotype association tests should be performed to most efficiently exploit the available degrees of freedom, focusing attention on those comparisons most likely to define functionally different haplotypes (Haviland et al., 1995). This type of analysis has been used to define interactions between heart disease and the apolipoprotein gene cluster (Haviland et al 1995) and Alzheimer's Disease and the Apo-E locus (Templeton 1995) among other studies, using populations as small as 50 to 100 individuals. The methods of Templeton have also been applied to measure the genetic determinants of variation in the angiotensin-I converting enzyme gene. (Keavney, B., McKenzie, C. A., Connoll, J.M.C., et al. Measured haplotype analysis of the angiotensin-I converting enzyme gene. *Human Molecular Genetics* 7: 1745-1751.)

*Methods for determining haplotypes*

The goal of haplotyping is to identify the common haplotypes at selected loci that have multiple sites of variance. Haplotypes are usually determined at the cDNA level. Several general approaches to identification of haplotypes can be employed. Haplotypes may also be estimated using computational methods or determined  
5 definitively using experimental approaches. Computational approaches generally include an expectation maximization (E-M) algorithm (see, for example: Excoffier and Slatkin, *Mol. Biol. Evol.* 1995) or a combination of Parsimony (see below) and E-M methods.

Haplotypes can be determined experimentally without requirement of a  
10 haplotyping method by genotyping samples from a set of pedigrees and observing the segregation of haplotypes. For example families collected by the Centre d'Etude du Polymorphisme Humaine (CEPH) can be used. Cell lines from these families are available from the Coriell Repository. This approach will be useful for cataloging common haplotypes and for validating methods on samples with known haplotypes.  
15 The set of haplotypes determined by pedigree analysis can be useful in computational methods, including those utilizing the E-M algorithm.

Haplotypes can also be determined directly from cDNA using the T4E7 procedure. T4E7 cleaves mismatched heteroduplex DNA at the site of the mismatch. If a heteroduplex contains only one mismatch, cleavage will result in the  
20 generation of two fragments. However, if a single heteroduplex (allele) contains two mismatches, cleavage will occur at two different sites resulting in the generation of three fragments. The appearance of a fragment whose size corresponds to the distance between the two cleavage sites is diagnostic of the two mismatches being present on the same strand (allele). Thus, T4E7 can be used to determine haplotypes  
25 in diploid cells.

An alternative method, allele specific PCR, may be used for haplotyping. The utility of allele specific PCR for haplotyping has already been established (Michalatos-Beloin et al., 1996; Chang et al. 1997). Opposing PCR primers are  
30 designed to cover two sites of variance (either adjacent sites or sites spanning one or more internal variances). Two versions of each primer are synthesized, identical to each other except for the 3' terminal nucleotide. The 3' terminal nucleotide is designed so that it will hybridize to one but not the other variant base. PCR amplification is then attempted with all four possible primer combinations in separate wells. Because Taq polymerase is very inefficient at extending 3'  
35 mismatches, the only samples which will be amplified will be the ones in which the two primers are perfectly matched for sequences on the same strand (allele). The presence or absence of PCR product allows haplotyping of diploid cell lines. At

most two of four possible reactions should yield products. This procedure has been successfully applied, for example, to haplotype the DPD amino acid polymorphisms.

Parsimony methods are also useful for classifying DNA sequences, haplotypes or phenotypic characters. Parsimony principle maintains that the best explanation for the observed differences among sequences, phenotypes (individuals, species) etc., is provided by the smallest number of evolutionary changes.

Alternatively, simpler hypotheses are preferable to explain a set of data or patterns, than more complicated ones, and *ad hoc* hypotheses should be avoided whenever possible (Molecular Systematics, Hillis et al., 1996). Parsimony methods thus operate by minimizing the number of evolutionary steps or mutations (changes from one sequence/character) required to account for a given set of data.

For example, supposing we want to obtain relationships among a set of sequences and construct a structure (tree/topology), we first count the minimum number of mutations that are required for explaining the observed evolutionary changes among a set of sequences. A structure (topology) is constructed based on this number. When once this number is obtained, another structure is tried. This process is continued for all reasonable number of structures. Finally, the structure that required the smallest number of mutational steps is chosen as the likely structure/evolutionary tree for the sequences studied.

#### D. Selection of Treatment Method Using Variance Information

##### 1. General

Once the presence or absence of a variance or variances in a gene or genes is shown to correlate with the efficacy or safety of a treatment method, that information can be used to select an appropriate treatment method for a particular patient. In the case of a treatment which is more likely to be effective when administered to a patient who has at least one copy of a gene with a particular variance or variances (in some cases the correlation with effective treatment is for patients who are homozygous for a variance or set of variances in a gene) than in patients with a different variance or set of variances, a method of treatment is selected (and/or a method of administration) which correlates positively with the particular variance presence or absence which provides the indication of effectiveness. As indicated in the Summary, such selection can involve a variety of different choices, and the correlation can involve a variety of different types of treatments, or choices of methods of treatment. In some cases, the selection may include choices between treatments or methods of administration where more than one method is likely to be effective, or where there is a range of expected effectiveness or different expected levels of contra-indication or deleterious effects.

In such cases the selection is preferably performed to select a treatment which will be as effective or more effective than other methods, while having a comparatively low level of deleterious effects. Similarly, where the selection is between method with differing levels of deleterious effects, preferably a method is selected which has low such effects but which is expected to be effective in the patient.

Alternatively, in cases where the presence or absence of the particular variance or variances is indicative that a treatment or method of administration is more likely to be ineffective or contra-indicated in a patient with that variance or variances, then such treatment or method of administration is generally eliminated for use in that patient.

## 2. Diagnostic Methods

Once a correlation between the presence and absence of at least one variance in a gene or genes and an indication of the effectiveness of a treatment, the determination of the presence or absence of that at least one variance provides diagnostic methods, which can be used as indicated in the Summary above to select methods of treatment, methods of administration of a treatment, methods of selecting a patient or patients for a treatment and others aspects in which the determination of the presence or absence of those variances provides useful information for selecting or designing or preparing methods or materials for medical use in the aspects of this invention. As previously stated, such variance determination or diagnostic methods can be performed in various ways as understood by those skilled in the art.

In certain variance determination methods, it is necessary or advantageous to amplify one or more nucleotide sequences in one or more of the genes identified herein. Such amplification can be performed by conventional methods, e.g., using polymerase chain reaction (PCR) amplification. Such amplification methods are well-known to those skilled in the art and will not be specifically described herein. For most applications relevant to the present invention, a sequence to be amplified includes at least one variance site, which is preferably a site or sites which provide variance information indicative of the effectiveness of a method of treatment or method of administration of a treatment, or effectiveness of a second method of treatment which reduces a deleterious effect of a first treatment method, or which enhances the effectiveness of a first method of treatment. Thus, for PCR, such amplification generally utilizes primer oligonucleotides which bind to or extend through at least one such variance site under amplification conditions.

For convenient use of the amplified sequence, e.g., for sequencing, it is beneficial that the amplified sequence be of limited length, but still long enough to

allow convenient and specific amplification. Thus, preferably the amplified sequence has a length as described in the Summary.

Also, in certain variance determination, it is useful to sequence one or more portions of a gene or genes, in particular, portions of the genes identified in this disclosure. As understood by persons familiar with nucleic acid sequencing, there are a variety of effective methods. In particular, sequencing can utilize dye termination methods and mass spectrometric methods. The sequencing generally involves a nucleic acid sequence which includes a variance site as indicated above in connection with amplification. Such sequencing can directly provide determination of the presence or absence of a particular variance or set of variances, e.g., a haplotype, by inspection of the sequence (visually or by computer). Such sequencing is generally conducted on PCR amplified sequences in order to provide sufficient signal for practical or reliable sequence determination.

Likewise, in certain variance determinations, it is useful to utilize a probe or probes. As previously described, such probes can be of a variety of different types.

## VII. Loss of Heterozygosity and Conditionally Essential Genes

Different environmental, pharmacological, and physical changes in the environment that result in homeostatic or compensatory responses in which genes that are not normally essential for cell survival or proliferation become essential are known in the art.

When LOH results in a difference in normal cell genotype vs. cancer cell genotype that affects a locus encoding a product affecting the cells' ability to survive in the presence of an environmental change, or a pharmaceutical or biological agent, or a physical factor, there is an opportunity to exploit a therapeutic window between cancer cells and normal cells. Below we describe specific examples of genes that (1) affect cell responses to altered environments, (2) are located on chromosomes that undergo LOH in cancer and (3) exist in two or more variant forms. These examples have been selected to illustrate how the therapeutic strategy described in this application would work with a variety of different alterations in chemical or physical environment. Example 20 describes a gene (Dihydropyrimidine Dehydrogenase) that mediates response to an altered chemical environment (presence of the toxic chemical 5-fluorouridine) by specifically transforming the chemical to an inactive metabolite. Example 27 describes a gene (Methylguanine methyltransferase) that mediates response to an altered chemical environment (presence of toxic chemicals such as nitrosourea or other alkylating agents) by removing methyl or alkyl adducts to DNA, the principal toxic lesion of these agents.

Example 21 describes a set of genes (Fanconi Anemia genes A,B,C,D,E,F,G and H) which mediate response to an altered chemical environment (presence of chemicals which cause DNA crosslinking, such as diepoxybutane, mitomycin C and cisplatinum) by repairing the crosslinks. Example 25 describes a set of genes (the DNA Dependent Protein Kinase Complex, including the DNA Dependent Protein Kinase catalytic subunit (DNA-PKcs), the DNA binding component (called Ku), made up of Ku-70 and Ku-86 kDa subunits, and the Ku-86 related protein Karp-1) that mediates repair of double stranded DNA breaks, such as occurs after x-irradiation. Example 22 describes a gene (asparagine synthase) that mediates response to an altered nutritional environment (absence of extracellular asparagine) which can be produced by an enzyme such as asparaginase, which hydrolyzes serum asparagine. Example 26 describes the Ataxia Telangiectasia gene, which is involved in response to ionizing radiation and radiomimetic chemicals. Other detailed examples include methionine synthase (Ex. 23) and methylthioadenosine phosphorylase (Ex. 24). Other examples include Poly (ADP) Ribose Polymerase (PARP), Glutathione-S- Transferase pi (GST-pi), NF-kappa B, Abl Kinase, 3-alkylguanine alkyltransferase, N-methylpurine DNA glycosylase (hydrolyzes the deoxyribose N-glycosidic bond to excise 3-methyladenine and 7-methylguanine from alkylating agent-damaged DNA polymers), OGG-1, MDR-1.

In addition to the direct use of conditionally essential (or essential) genes in allele-specific inhibitor applications, the information provided by the LOH status of a gene. For example, in some cases, the effect of LOH can be a gene dosage effect. This can additionally be combined with a reduced activity associated with particular forms of the gene. Either or both types of information can be used to identify patients who would be expected to respond differently to a treatment targeting that gene than would patients with two copies of the gene, or with at least one copy of a different form of the gene than remained after LOH. To illustrate, a patient may be heterozygous for a high activity allele and a low activity allele. LOH in cancer cells could remove either the high activity allele or the low activity allele, leaving only the other allele in cancer cells in the patient, while the normal cells would have intermediate activity due the presence of both alleles. As a result, a therapy targeting or otherwise involving that gene in the response to treatment would be expected to result in variation in response between the normal cells and the cancer cells in the patient. If the low activity allele correlated with high response to the therapy, then it would be expected that the anti-cancer treatment would be more effective in a patient with such LOH than in a patient in whom cancer cells had not undergone LOH with respect to that gene.

Indeed, LOH assays for particular genes can also be used as surrogate assays for other LOH of other genes located near the marker gene. Thus, the marker gene can, for example, be used in connection with LOH-related effects or evaluations of other nearby genes. Such genes can include genes in the same pathway, as those genes are often located in close proximity on the same chromosome.

It has been shown that LOH at tumor suppressor genes correlates with anticancer chemotherapy response. Thus, LOH information on tumor suppressor genes can also be used in connection with LOH and/or pharmacogenetic information about other genes. As a result, it is beneficial to determine both the LOH status of the tumor suppressor gene or genes and one or more additional genes.

Together, or separately, the LOH information and the variance-based pharmacogenetic information can be used to identify patient subset that will respond differently to a particular therapy related to particular genes and/or to select appropriate therapies for patients based on the forms of the gene or genes in disease cells and normal cells.

## **VII. Pharmaceutical Compositions, Including Pharmaceutical Compositions Adapted to be Preferentially Effective in Patients Having Particular Genetic Characteristics**

### **A. General**

The methods of the present invention, in many cases will utilize conventional pharmaceutical compositions, but will allow more advantageous and beneficial use of those compositions due to the ability to identify patients who are likely to benefit from a particular treatment or to identify patients for whom a particular treatment is less likely to be effective or for whom a particular treatment is likely to produce undesirable or intolerable effects. However, in some cases, it is advantageous to utilize compositions which are adapted to be preferentially effective in patients who possess particular genetic characteristics, i.e., in whom a particular variance or variances in one or more genes is present or absent (depending on whether the presence or the absence of the variance or variances in a patient is correlated with an increased expectation of beneficial response). Thus, for example, the presence of a particular variance or variances may indicate that a patient can beneficially receive a significantly higher dosage of a drug than a patient having a different

### **B. Regulatory Indications and Restrictions**

The sale and use of drugs and the use of other treatment methods usually are subject to certain restrictions by a government regulatory agency charged with



ensuring the safety and efficacy of drugs and treatment methods for medical use, and approval is based on particular indications. In the present invention it is found that variability in patient response or patient tolerance of a drug or other treatment often correlates with the presence or absence of particular variances in particular genes.

5 Thus, it is expected that such a regulatory agency may indicate that the approved indications for use of a drug with a variance-related variable response or toleration include use only in patients in whom the drug will be effective, and/or for whom the administration of the drug will not have intolerable deleterious effects, such as excessive toxicity or unacceptable side-effects. Conversely, the drug may be given  
10 for an indication that it may be used in the treatment of a particular disease or condition where the patient has at least one copy of a particular variance, variances, or variant form of a gene. Even if the approved indications are not narrowed to such groups, the regulatory agency may suggest use limited to particular groups or excluding particular groups or may state advantages of use or exclusion of such  
15 groups or may state a warning on the use of the drug in certain groups. Consistent with such suggestions and indications, such an agency may suggest or recommend the use of a diagnostic test to identify the presence or absence of the relevant variances in the prospective patient. Such diagnostic methods are described in this description. Generally, such regulatory suggestion or indication is provided in a  
20 product insert or label, and is generally reproduced in references such as the Physician's Desk Reference (PDR). Thus, this invention also includes drugs or pharmaceutical compositions which carry such a suggestion or statement of indication or warning or suggestion for a diagnostic test, and which may also be packaged with an insert or label stating the suggestion or indication or warning or  
25 suggestion for a diagnostic test.

In accord with the possible variable treatment responses, an indication or suggestion can specify that a patient be heterozygous, or alternatively, homozygous for a particular variance or variances or variant form of a gene. Alternatively, an indication or suggestion may specify that a patient have no more than one copy, or  
30 zero copies, of a particular variance, variances, or variant form of a gene.

A regulatory indication or suggestion may concern the variances or variant forms of a gene in normal cells of a patient and/or in cells involved in the disease or condition. For example, in the case of a cancer treatment, the response of the cancer cells can depend on the form of a gene remaining in cancer cells following loss of  
35 heterozygosity affecting that gene. Thus, even though normal cells of the patient may contain a form of the gene which correlates with effective treatment response, the absence of that form in cancer cells will mean that the treatment would be less likely to be effective in that patient than in another patient who retained in cancer

cells the form of the gene which correlated with effective treatment response. Those skilled in the art will understand whether the variances or gene forms in normal or disease cells are most indicative of the expected treatment response, and will generally utilize a diagnostic test with respect to the appropriate cells. Such a cell type indication or suggestion may also be contained in a regulatory statement, e.g., on a label or in a product insert.

C. Preparation and Administration of Drugs and Pharmaceutical Compositions Including Pharmaceutical Compositions Adapted to be Preferentially Effective in Patients Having Particular Genetic Characteristics

A particular compound useful in this invention can be administered to a patient either by itself, or in pharmaceutical compositions where it is mixed with suitable carriers or excipient(s). In treating a patient exhibiting a disorder of interest, a therapeutically effective amount of a agent or agents such as these is administered. A therapeutically effective dose refers to that amount of the compound that results in amelioration of one or more symptoms or a prolongation of survival in a patient.

Toxicity and therapeutic efficacy of such compounds can be determined by standard pharmaceutical procedures in cell cultures or experimental animals, e.g., for determining the LD<sub>50</sub> (the dose lethal to 50% of the population) and the ED<sub>50</sub> (the dose therapeutically effective in 50% of the population). The dose ratio between toxic and therapeutic effects is the therapeutic index and it can be expressed as the ratio LD<sub>50</sub>/ED<sub>50</sub>. Compounds which exhibit large therapeutic indices are preferred. The data obtained from these cell culture assays and animal studies can be used in formulating a range of dosage for use in human. The dosage of such compounds lies preferably within a range of circulating concentrations that include the ED<sub>50</sub> with little or no toxicity. The dosage may vary within this range depending upon the dosage form employed and the route of administration utilized.

For any compound used in the method of the invention, the therapeutically effective dose can be estimated initially from cell culture assays. For example, a dose can be formulated in animal models to achieve a circulating plasma concentration range that includes the IC<sub>50</sub> as determined in cell culture. Such information can be used to more accurately determine useful doses in humans. Levels in plasma may be measured, for example, by HPLC.

The exact formulation, route of administration and dosage can be chosen by the individual physician in view of the patient's condition. (See e.g. Fingl et. al., in The Pharmacological Basis of Therapeutics, 1975, Ch. 1 p.1). It should be noted that the attending physician would know how to and when to terminate, interrupt, or adjust administration due to toxicity, or to organ dysfunctions. Conversely, the

attending physician would also know to adjust treatment to higher levels if the clinical response were not adequate (precluding toxicity). The magnitude of an administered dose in the management of disorder of interest will vary with the severity of the condition to be treated and the route of administration. The severity  
5 of the condition may, for example, be evaluated, in part, by standard prognostic evaluation methods. Further, the dose and perhaps dose frequency, will also vary according to the age, body weight, and response of the individual patient. A program comparable to that discussed above may be used in veterinary medicine.

Depending on the specific conditions being treated, such agents may be  
10 formulated and administered systemically or locally. Techniques for formulation and administration may be found in Remington's Pharmaceutical Sciences, 18th ed., Mack Publishing Co., Easton, PA (1990). Suitable routes may include oral, rectal, transdermal, vaginal, transmucosal, or intestinal administration; parenteral delivery, including intramuscular, subcutaneous, intramedullary injections, as well as  
15 intrathecal, direct intraventricular, intravenous, intraperitoneal, intranasal, or intraocular injections, just to name a few.

For injection, the agents of the invention may be formulated in aqueous solutions, preferably in physiologically compatible buffers such as Hanks's solution, Ringer's solution, or physiological saline buffer. For such transmucosal  
20 administration, penetrants appropriate to the barrier to be permeated are used in the formulation. Such penetrants are generally known in the art.

Use of pharmaceutically acceptable carriers to formulate the compounds herein disclosed for the practice of the invention into dosages suitable for systemic administration is within the scope of the invention. With proper choice of carrier  
25 and suitable manufacturing practice, the compositions of the present invention, in particular, those formulated as solutions, may be administered parenterally, such as by intravenous injection. The compounds can be formulated readily using pharmaceutically acceptable carriers well known in the art into dosages suitable for oral administration. Such carriers enable the compounds of the invention to be  
30 formulated as tablets, pills, capsules, liquids, gels, syrups, slurries, suspensions and the like, for oral ingestion by a patient to be treated.

Agents intended to be administered intracellularly may be administered using techniques well known to those of ordinary skill in the art. For example, such agents may be encapsulated into liposomes, then administered as described above.

35 Liposomes are spherical lipid bilayers with aqueous interiors. All molecules present in an aqueous solution at the time of liposome formation are incorporated into the aqueous interior. The liposomal contents are both protected from the external microenvironment and, because liposomes fuse with cell membranes, are efficiently

delivered into the cell cytoplasm. Additionally, due to their hydrophobicity, small organic molecules may be directly administered intracellularly.

Pharmaceutical compositions suitable for use in the present invention include compositions wherein the active ingredients are contained in an effective amount to achieve its intended purpose. Determination of the effective amounts is well within the capability of those skilled in the art, especially in light of the detailed disclosure provided herein. In addition to the active ingredients, these pharmaceutical compositions may contain suitable pharmaceutically acceptable carriers comprising excipients and auxiliaries which facilitate processing of the active compounds into preparations which can be used pharmaceutically. The preparations formulated for oral administration may be in the form of tablets, dragees, capsules, or solutions. The pharmaceutical compositions of the present invention may be manufactured in a manner that is itself known, *e.g.*, by means of conventional mixing, dissolving, granulating, dragee-making, levitating, emulsifying, encapsulating, entrapping or lyophilizing processes.

Pharmaceutical formulations for parenteral administration include aqueous solutions of the active compounds in water-soluble form. Additionally, suspensions of the active compounds may be prepared as appropriate oily injection suspensions. Suitable lipophilic solvents or vehicles include fatty oils such as sesame oil, or synthetic fatty acid esters, such as ethyl oleate or triglycerides, or liposomes. Aqueous injection suspensions may contain substances which increase the viscosity of the suspension, such as sodium carboxymethyl cellulose, sorbitol, or dextran. Optionally, the suspension may also contain suitable stabilizers or agents which increase the solubility of the compounds to allow for the preparation of highly concentrated solutions.

Pharmaceutical preparations for oral use can be obtained by combining the active compounds with solid excipient, optionally grinding a resulting mixture, and processing the mixture of granules, after adding suitable auxiliaries, if desired, to obtain tablets or dragee cores. Suitable excipients are, in particular, fillers such as sugars, including lactose, sucrose, mannitol, or sorbitol; cellulose preparations such as, for example, maize starch, wheat starch, rice starch, potato starch, gelatin, gum tragacanth, methyl cellulose, hydroxypropylmethyl-cellulose, sodium carboxymethylcellulose, and/or polyvinylpyrrolidone (PVP). If desired, disintegrating agents may be added, such as the cross-linked polyvinyl pyrrolidone, agar, or alginic acid or a salt thereof such as sodium alginate. Dragee cores are provided with suitable coatings. For this purpose, concentrated sugar solutions may be used, which may optionally contain gum arabic, talc, polyvinyl pyrrolidone, carbopol gel, polyethylene glycol, and/or titanium dioxide, lacquer solutions, and

suitable organic solvents or solvent mixtures. Dyestuffs or pigments may be added to the tablets or dragee coatings for identification or to characterize different combinations of active compound doses.

Pharmaceutical preparations which can be used orally include push-fit capsules made of gelatin, as well as soft, sealed capsules made of gelatin and a plasticizer, such as glycerol or sorbitol. The push-fit capsules can contain the active ingredients in admixture with filler such as lactose, binders such as starches, and/or lubricants such as talc or magnesium stearate and, optionally, stabilizers. In soft capsules, the active compounds may be dissolved or suspended in suitable liquids, such as fatty oils, liquid paraffin, or liquid polyethylene glycols. In addition, stabilizers may be added.

The invention described herein features methods for determining the appropriate identification of a patient diagnosed with a neurological disease or neurological dysfunction based on an analysis of the patient's allele status for a gene listed in Tables 1-6, 12-17, and 18-23. Specifically, the presence of at least one allele indicates that a patient will respond to a candidate therapeutic intervention aimed at treating clinical symptoms. In a preferred approach, the patient's allele status is rapidly diagnosed using a sensitive PCR assay and a treatment protocol is rendered. The invention also provides a method for forecasting patient outcome and the suitability of the patient for entering a clinical drug trial for the testing of a candidate therapeutic intervention for a disease, condition, or dysfunction as identified herein.

The findings described herein indicate the predictive value of the target allele in identifying patients at risk for a disease or disorder as identified for aspects herein. In addition, because the underlying mechanism influenced by the allele status is not disease-specific, the allele status is suitable for making patient predictions for diseases not affected by the pathway as well.

The following examples, which describe exemplary techniques and experimental results, are provided for the purpose of illustrating the invention, and should not be construed as limiting.

### **Example 1**

#### **Method for Producing cDNA**

In order to identify sequence variances in a gene by laboratory methods it is in some instances useful to produce cDNA(s) from multiple human subjects. (In other instances it may be preferable to study genomic DNA.). Methods for producing cDNA are known to those skilled in the art, as are methods for amplifying and sequencing the cDNA or portions thereof. An example of a useful cDNA

production protocol is provided below. As recognized by those skilled in the art, other specific protocols can also be used.

#### cDNA Production

\*\* Make sure that all tubes and pipette tips are RNase-free. (Bake them overnight at 100°C in a vacuum oven to make them RNase-free.)

1. Add the following to a RNase-free 0.2 ml micro-amp tube and mix gently:

24 ul water (DEPC treated)  
12 ul RNA (1ug/ul)  
12 ul random hexamers(50 ng/ul)

2. Heat the mixture to 70°C for ten minutes.

3. Incubate on ice for 1 minute.

4. Add the following:

16 ul 5 X Synthesis Buffer  
8 ul 0.1 M DTT  
4 ul 10 mM dNTP mix (10 mM each dNTP)  
4 ul SuperScript RT II enzyme

Pipette gently to mix.

5. Incubate at 42°C for 50 minutes.

6. Heat to 70°C for ten minutes to kill the enzyme, then place it on ice.

7. Add 160 ul of water to the reaction so that the final volume is 240 ul.

8. Use PCR to check the quality of the cDNA. Use primer pairs that will give a ~800 base pair long piece. See "PCR Optimization" for the PCR protocol.

The following chart shows the reagent amounts for a 20 ul reaction, a 80 ul reaction, and a batch of 39 (which makes enough mix for 36) reactions:

|  |                |                |                 |  |
|--|----------------|----------------|-----------------|--|
|  | 20 ul X 1 tube | 80 ul X 1 tube | 80ul X 39 tubes |  |
|--|----------------|----------------|-----------------|--|

|                  |      |       |     |                  |
|------------------|------|-------|-----|------------------|
| Water            | 6 ul | 24 ul | 936 | water            |
| RNA              | 3 ul | 12 ul |     | RNA              |
| random hexamers  | 3 ul | 12 ul | 468 | random hexamers  |
| synthesis buffer | 4 ul | 16 ul | 624 | synthesis buffer |
| 0.1 M DTT        | 2 ul | 8 ul  | 312 | 0.1 M DTT        |
| 10mM dNTP        | 1 ul | 4 ul  | 156 | 10mM dNTP        |
| SSRT             | 1 ul | 4 ul  | 156 | SSRT             |

### **Example 2**

#### **Method for Detecting Variances by Single Strand Conformation Polymorphism (SSCP) Analysis**

This example describes the SSCP technique for identification of sequence variances of genes. SSCP is usually paired with a DNA sequencing method, since the SSCP method does not provide the nucleotide identity of variances. One useful sequencing method, for example, is DNA cycle sequencing of  $^{32}\text{P}$  labeled PCR products using the Femtomole DNA cycle sequencing kit from Promega (WI) and the instructions provided with the kit. Fragments are selected for DNA sequencing based on their behavior in the SSCP assay.

Single strand conformation polymorphism screening is a widely used technique for identifying an discriminating DNA fragments which differ from each other by as little as a single nucleotide. As originally developed by Orita et al. (Detection of polymorphisms of human DNA by gel electrophoresis as single-strand conformation polymorphisms. *Proc Natl Acad Sci U S A.* 86(8):2766-70, 1989), the technique was used on genomic DNA, however the same group showed that the technique works very well on PCR amplified DNA as well. In the last 10 years the technique has been used in hundreds of published papers, and modifications of the technique have been described in dozens of papers. The enduring popularity of the technique is due to (1) a high degree of sensitivity to single base differences (>90%) (2) a high degree of selectivity, measured as a low frequency of false positives, and (3) technical ease. SSCP is almost always used together with DNA sequencing because SSCP does not directly provide the sequence basis of differential fragment mobility. The basic steps of the SSCP procedure are described below.

When the intent of SSCP screening is to identify a large number of gene variances it is useful to screen a relatively large number of individuals of different racial, ethnic and/or geographic origins. For example, 32 or 48 or 96 individuals is a convenient number to screen because gel electrophoresis apparatus are available with 96 wells (Applied Biosystems Division of Perkin Elmer Corporation), allowing 3 X 32, 2 X 48 or 96 samples to be loaded per gel.

The 32 (or more) individuals screened should be representative of most of the worlds major populations. For example, an equal distribution of Africans, Europeans and Asians constitutes a reasonable screening set. One useful source of cell lines from different populations is the Coriell Cell Repository (Camden, NJ), which sells EBV immortalized lymphoblastoid cells obtained from several thousand subjects, and includes the racial/ethnic/geographic background of cell line donors in its catalog. Alternatively, a panel of cDNAs can be isolated from any specific target population.

SSCP can be used to analyze cDNAs or genomic DNAs. For many genes cDNA analysis is preferable because for many genes the full genomic sequence of the target gene is not available, however, this circumstance will change over the next few years. To produce cDNA requires RNA. Therefore each cell lines is grown to mass culture and RNA is isolated using an acid/phenol protocol, sold in kit form as Trizol by Life Technologies (Gaithersburg, MD). The unfractionated RNA is used to produce cDNA by the action of a modified Maloney Murine Leukemia Virus Reverse Transcriptase, purchased in kit form from Life Technologies (Superscript II kit). The reverse transcriptase is primed with random hexamer primers to initiate cDNA synthesis along the whole length of the RNAs. This proved useful later in obtaining good PCR products from the 5' ends of some genes. Alternatively, oligodT can be used to prime cDNA synthesis.

Material for SSCP analysis can be prepared by PCR amplification of the cDNA in the presence of one  $\alpha$   $^{32}\text{P}$  labeled dNTP (usually  $\alpha$   $^{32}\text{P}$  dCTP). Usually the concentration of nonradioactive dCTP is dropped from 200  $\mu\text{M}$  (the standard concentration for each of the four dNTPs) to about 100  $\mu\text{M}$ , and  $^{32}\text{P}$  dCTP is added to a concentration of about 0.1-0.3  $\mu\text{M}$ . This involves adding a 0.3- 1  $\mu\text{l}$  (3-10  $\mu\text{Ci}$ ) of  $^{32}\text{P}$  cCTP to a 10  $\mu\text{l}$  PCR reaction. Radioactive nucleotides can be purchased from DuPont/New England Nuclear.

The customary practice is to amplify about 200 base pair PCR products for SSCP, however, an alternative approach is to amplify about 0.8-1.4 kb fragments and then use several cocktails of restriction endonucleases to digest those into smaller fragments of about 0.1-0.4kb, aiming to have as many fragments as possible between .15 and .3 kb. The digestion strategy has the advantage that less PCR is required, reducing both time and costs. Also, several different restriction enzyme digests can be performed on each set of samples (for example 96 cDNAs), and then each of the digests can be run separately on SSCP gels. This redundant method (where each nucleotide is surveyed in three different fragments) reduces both the false negative and false positive rates. For example: a site of variance might lie within 2 bases of the end of a fragment in one digest, and as a result not affect the



conformation of that strand; the same variance, in a second or third digest, would likely lie in a location more prone to affect strand folding, and therefore be detected by SSCP.

After digestion, the radiolabelled PCR products are diluted 1:5 by adding  
5 formamide load buffer (80% formamide, 1X SSCP gel buffer) and then denatured by heating to 90°C for 10 minutes, and then allowed to renature by quickly chilling on ice. This procedure (both the dilution and the quick chilling) promotes intra- (rather than inter-) strand association and secondary structure formation. The secondary  
10 structure of the single strands influences their mobility on nondenaturing gels, presumably by influencing the number of collisions between the molecule and the gel matrix (i.e., gel sieving). Even single base differences consistently produce changes in intrastrand folding sufficient to register as mobility differences on SSCP.

The single strands were then resolved on two gels, one a 5.5% acrylamide, 0.5X TBE gel, the other an 8% acrylamide, 10% glycerol, 1X TTE gel. (Other gel  
15 recipes are known to those skilled in the art.) The use of two gels provides a greater opportunity to recognize mobility differences. Both glycerol and acrylamide concentration have been shown to influence SSCP performance. By routinely analyzing three different digests under two gel conditions (effectively 6 conditions), and by looking at both strands under all 6 conditions, one can achieve a 12-fold  
20 sampling of each base pair of cDNA. However, if the goal is to rapidly survey many genes or cDNAs then a less redundant procedure would be optimal.

**Example 3****Method for Detecting Variances by T4 endonuclease VII (T4E7) mismatch cleavage method**

The enzyme T4 endonuclease VII is derived from the bacteriophage T4. T4 endonuclease VII is used by the bacteriophage to cleave branched DNA intermediates which form during replication so the DNA can be processed and packaged. T4 endonuclease can also recognize and cleave heteroduplex DNA containing single base mismatches as well as deletions and insertions. This activity of the T4 endonuclease VII enzyme can be exploited to detect sequence variances present in the general population.

The following are the major steps involved in identifying sequence variations in a candidate gene by T4 endonuclease VII mismatch cleavage:

1. Amplification by the polymerase chain reaction (PCR) of 400-600 bp regions of the candidate gene from a panel of DNA samples. The DNA samples can either be cDNA or genomic DNA and will represent some cross section of the world population.
2. Mixing of a fluorescently labeled probe DNA with the sample DNA. Heating and cooling the mixtures causing heteroduplex formation between the probe DNA and the sample DNA.
3. Addition of T4 endonuclease VII to the heteroduplex DNA samples. T4 endonuclease will recognize and cleave at sequence variance mismatches formed in the heteroduplex DNA.
4. Electrophoresis of the cleaved fragments on an ABI sequencer to determine the site of cleavage.
5. Sequencing of a subset of PCR fragments identified by T4 endonuclease VI to contain variances to establish the specific base variation at that location.

A more detailed description of the procedure is as follows:

A candidate gene sequence is downloaded from an appropriate database. Primers for PCR amplification are designed which will result in the target sequence being divided into amplification products of between 400 and 600 bp. There will be a minimum of a 50 bp of overlap not including the primer sequences between the 5' and 3' ends of adjacent fragments to ensure the detection of variances which are located close to one of the primers.

Optimal PCR conditions for each of the primer pairs is determined experimentally. Parameters including but not limited to annealing temperature, pH, MgCl<sub>2</sub> concentration, and KCl concentration will be varied until conditions for optimal PCR amplification are established. The PCR conditions derived for each

primer pair is then used to amplify a panel of DNA samples (cDNA or genomic DNA) which is chosen to best represent the various ethnic backgrounds of the world population or some designated subset of that population.

One of the DNA samples is chosen to be used as a probe. The same PCR  
5 conditions used to amplify the panel are used to amplify the probe DNA. However, a fluorescently labeled nucleotide is included in the deoxy-nucleotide mix so that a percentage of the incorporated nucleotides will be fluorescently labeled.

The labeled probe is mixed with the corresponding PCR products from each  
10 of the DNA samples and then heated and cooled rapidly. This allows the formation of heteroduplexes between the probe and the PCR fragments from each of the DNA samples. T4 endonuclease VII is added directly to these reactions and allowed to incubate for 30 min. at 37 C. 10 ul of the Formamide loading buffer is added directly to each of the samples and then denatured by heating and cooling. A  
15 portion of each of these samples is electrophoresed on an ABI 377 sequencer. If there is a sequence variance between the probe DNA and the sample DNA a mismatch will be present in the heteroduplex fragment formed. The enzyme T4 endonuclease VII will recognize the mismatch and cleave at the site of the mismatch. This will result in the appearance of two peaks corresponding to the two  
20 cleavage products when run on the ABI 377 sequencer.

Fragments identified as containing sequencing variances are subsequently  
sequenced using conventional methods to establish the exact location and sequence  
variance.

**Example 4****Method for Detecting Variances by DNA sequencing.**

Sequencing by the Sanger dideoxy method or the Maxim Gilbert chemical cleavage method is widely used to determine the nucleotide sequence of genes. Presently, a worldwide effort is being put forward to sequence the entire human genome. The Human Genome Project as it is called has already resulted in the identification and sequencing of many new human genes. Sequencing can not only be used to identify new genes, but can also be used to identify variations between individuals in the sequence of those genes.

The following are the major steps involved in identifying sequence variations in a candidate gene by sequencing:

1. Amplification by the polymerase chain reaction (PCR) of 400-700 bp regions of the candidate gene from a panel of DNA samples. The DNA samples can either be cDNA or genomic DNA and will represent some cross section of the world population.
2. Sequencing of the resulting PCR fragments using the Sanger dideoxy method. Sequencing reactions are performed using fluorescently labeled dideoxy terminators and fragments are separated by electrophoresis on an ABI 377 sequencer or its equivalent.
3. Analysis of the resulting data from the ABI 377 sequencer using software programs designed to identify sequence variations between the different samples analyzed.

A more detailed description of the procedure is as follows:

A candidate gene sequence is downloaded from an appropriate database. Primers for PCR amplification are designed which will result in the target sequence being divided into amplification products of between 400 and 700 bp. There will be a minimum of a 50 bp of overlap not including the primer sequences between the 5' and 3' ends of adjacent fragments to ensure the detection of variances which are located close to one of the primers.

Optimal PCR conditions for each of the primer pairs is determined experimentally. Parameters including but not limited to annealing temperature, pH, MgCl<sub>2</sub> concentration, and KCl concentration will be varied until conditions for optimal PCR amplification are established. The PCR conditions derived for each primer pair is then used to amplify a panel of DNA samples (cDNA or genomic

DNA) which is chosen to best represent the various ethnic backgrounds of the world population or some designated subset of that population.

PCR reactions are purified using the QIAquick 8 PCR purification kit (Qiagen cat# 28142) to remove nucleotides, proteins and buffers. The PCR reactions are mixed with 5 volumes of Buffer PB and applied to the wells of the QIAquick strips. The liquid is pulled through the strips by applying a vacuum. The wells are then washed two times with 1 ml of buffer PE and allowed to dry for 5 minutes under vacuum. The PCR products are eluted from the strips using 60 ul of elution buffer.

The purified PCR fragments are sequenced in both directions using the Perkin Elmer ABI Prism™ Big Dye™ terminator Cycle Sequencing Ready Reaction Kit (Cat# 4303150). The following sequencing reaction is set up: 8.0 ul Terminator Ready Reaction Mix, 6.0 ul of purified PCR fragment, 20 picomoles of primer, deionized water to 20 ul. The reactions are run through the following cycles 25 times: 96°C for 10 second, annealing temperature for that particular PCR product for 5 seconds, 60°C for 4 minutes.

The above sequencing reactions are ethanol precipitated directly in the PCR plate, washed with 70% ethanol, and brought up in a volume of 6 ul of formamide dye. The reactions are heated to 90°C for 2 minutes and then quickly cooled to 4°C. 1 ul of each sequencing reaction is then loaded and run on an ABI 377 sequencer.

The output for the ABI sequencer appears as a series of peaks where each of the different nucleotides. A, C, G, and T appear as a different color. The nucleotide at each position in the sequence is determined by the most prominent peak at each location. Comparison of each of the sequencing outputs for each sample can be examined using software programs to determine the presence of a variance in the sequence. One example of heterozygote detection using sequencing with dye labeled terminators is described by Kwok *et. al.* (Kwok, P.-Y.; Carlson, C.; Yager, T.D., Ankener, W., and D. A. Nickerson, *Genomics* 23, 138-144, 1994). The software compares each of the normalized peaks between all the samples base by base and looks for a 40% decrease in peak height and the concomitant appearance of a new peak underneath. Possible variances flagged by the software are further analyzed visually to confirm their validity.

**Example 5****Hardy-Weinberg equilibrium**

Evolution is the process of change and diversification of organisms through time, and evolutionary change affects morphology, physiology and reproduction of organisms, including humans. These evolutionary changes are the result of changes in the underlying genetic or hereditary material. Evolutionary changes in a group of interbreeding individuals or Mendelian population, or simply populations, are described in terms of changes in the frequency of genotypes and their constituent alleles. Genotype frequencies for any given generation is the result of the mating among members (genotypes) of their previous generation. Thus, the expected proportion of genotypes from a random union of individuals in a given population is essential for describing the total genetic variation for a population of any species. For example, the expected number of genotypes that could form from the random union of two alleles, A and a, of a gene are AA, Aa and aa. The expected frequency of genotypes in a large, random mating population was discovered to remain constant from generation to generation; or achieve Hardy-Weinberg equilibrium, named after its discoverers. The expected genotypic frequencies of alleles A and a (AA, 2Aa, aa) are conventionally described in terms of  $p^2 + 2pq + q^2$  in which p and q are the allele frequencies of A and a. In this equation ( $p^2 + 2pq + q^2 = 1$ ), p is defined as the frequency of one allele and q as the frequency of another allele for a trait controlled by a pair of alleles (A and a). In other words, p equals all of the alleles in individuals who are homozygous dominant (AA) and half of the alleles in individuals who are heterozygous (Aa) for this trait. In mathematical terms, this is

$$p = AA + \frac{1}{2}Aa$$

Likewise, q equals the other half of the alleles for the trait in the population, or

$$q = aa + \frac{1}{2}Aa$$

Because there are only two alleles in this case, the frequency of one plus the frequency of the other must equal 100%, which is to say

$$p + q = 1$$

Alternatively,

$$p = 1 - q \text{ OR } q = 1 - p$$

All possible combinations of two alleles can be expressed as:

$$(p + q)^2 = 1$$

or more simply,

$$p^2 + 2pq + q^2 = 1$$

In this equation, if p is assumed to be dominant, then  $p^2$  is the frequency of homozygous dominant (AA) individuals in a population, 2pq is the frequency of

heterozygous (Aa) individuals, and  $q^2$  is the frequency of homozygous recessive (aa) individuals.

From observations of phenotypes, it is usually only possible to know the frequency of homozygous dominant or recessive individuals, because both dominant and recessives will express the distinguishable traits. However, the Hardy-Weinberg equation allows us to determine the expected frequencies of all the genotypes, if only p or q is known. Knowing p and q, it is a simple matter to plug these values into the Hardy-Weinberg equation ( $p^2 + 2pq + q^2 = 1$ ). This then provides the frequencies of all three genotypes for the selected trait within the population.

This illustration shows Hardy-Weinberg frequency distributions for the genotypes AA, Aa, and aa at all values for frequencies of the alleles, p and q. It should be noted that the proportion of heterozygotes increases as the values of p and q approach 0.5.

#### *Linkage disequilibrium*

Linkage is the tendency of genes or DNA sequences (e.g. SNPs) to be inherited together as a consequence of their physical proximity on a single chromosome. The closer together the markers are, the lower the probability that they will be separated during DNA crossing over, and hence the greater the probability that they will be inherited together. Suppose a mutational event introduces a "new" allele in the close proximity of a gene or an allele. The new allele will tend to be inherited together with the alleles present on the "ancestral," chromosome or haplotype. However, the resulting association, called linkage disequilibrium, will decline over time due to recombination. Linkage disequilibrium has been used to map disease genes. In general, both allele and haplotype frequencies differ among populations. Linkage disequilibrium is varied among the populations, being absent in some and highly significant in others.

#### *Quantification of the relative risk of observable outcomes of a Pharmacogenetics Trial*

Let PlaR be the placebo response rate (0% ( PlaR ( 100%) and TntR be the treatment response rate (0% ( TntR ( 100%) of a classical clinical trial. ObsRR is defined as the relative risk between TntR and PlaR:

$$\text{ObsRR} = \text{TntR} / \text{PlaR}.$$

Suppose that in the treatment group there is a polymorphism in relation to drug metabolism such as the treatment response rate is different for each genotypic subgroup of patients. Let q be the allele a frequency of a recessive biallelic locus (e.g. SNP) and  $p = 1 - q$  the allele A frequency. Following Hardy-Weinberg

equilibrium, the relative frequency of homozygous and heterozygous patients are as follow:

$$AA: p^2 \qquad Aa: 2pq \qquad aa: q^2$$

with

$$(p^2 + 2pq + q^2) = 1.$$

Let's define AAR, AaR, aaR as respectively the response rates of the AA, Aa and aa patients. We have the following relationship:

$$TntR = AAR \cdot p^2 + AaR \cdot 2pq + aaR \cdot q^2.$$

Suppose that the aa genotypic group of patients has the lowest response rate, i.e. a response rate equal to the placebo response rate (which means that the polymorphism has no impact on natural disease evolution but only on drug action) and let's define ExpRR as the relative risk between AAR and aaR, as

$$ExpRR = AAR / aaR.$$

From the previous equations, we have the following relationships:

$$ObsRR (ExpRR (1/PlaR$$

$$TntR / PlaR = (AAR \cdot p^2 + AaR \cdot 2pq + aaR \cdot q^2) / PlaR$$

The maximum of the expected relative risk, max(ExpRR), corresponding to the case of heterozygous patients having the same response rate as the placebo rate, is such that:

$$ObsRR = ExpRR \cdot p^2 + 2pq + q^2 \quad \Leftrightarrow \quad ExpRR = (ObsRR - 2pq - q^2) / p^2$$

The minimum of the expected relative risk, min(ExpRR), corresponding to the case of heterozygous patients having the same response rate as the homozygous non-affected patients, is such that:

$$ObsRR = ExpRR \cdot (p^2 + 2pq) + q^2 \quad \Leftrightarrow \quad ExpRR = (ObsRR - q^2) / (p^2 + 2pq)$$

For example, if  $q = 0.4$ ,  $PlaR = 40\%$  and  $ObsRR = 1.5$  (i.e.  $TntR = 60\%$ ), then  $1.6 (ExpRR (2.4$ . This means that the best treatment response rate we can expect in a genotypic subgroup of patients in these conditions would be 95.6% instead of 60%.

This can also be expressed in terms of maximum potential gain between the observed difference in response rates ( $TntR - PlaR$ ) without any pharmacogenetic hypothesis and the maximum expected difference in response rates ( $(\max(ExpRR) \cdot PlaR - TntR)$  with a strong pharmacogenetic hypothesis:

$$(\max(ExpRR) \cdot PlaR - TntR) = [(ObsRR - 2pq - q^2) / p^2] \cdot PlaR - TntR$$

$$\Leftrightarrow (\max(ExpRR) \cdot PlaR - TntR) = [TntR - PlaR \cdot (2pq + q^2) - TntR \cdot p^2] / p^2$$

$$\Leftrightarrow (\max(ExpRR) \cdot PlaR - TntR) = [TntR \cdot (1 - p^2) - PlaR \cdot (2pq + q^2)] / p^2$$

$$\Leftrightarrow (\max(ExpRR) \cdot PlaR - TntR) = [(1 - p^2) / p^2] \cdot (TntR - PlaR)$$



that is for the previous example,

$$(95.6\% - 60\%) = [(1 - 0.62)/0.62] * (60\% - 40\%) = 35.6\%$$

Suppose that, instead of one SNP, we have  $p$  loci of SNPs for one gene. This means that we have  $2p$  possible haplotypes for this gene and  $(2p)(2p-1)/2$  possible genotypes. And with 2 genes with  $p_1$  and  $p_2$  SNP loci, we have  $[(2p_1)(2p_1-1)/2] * [(2p_2)(2p_2-1)/2]$  possibilities; and so on. Examining haplotypes instead of combinations of SNPs is especially useful when there is linkage disequilibrium enough to reduce the number of combinations to test, but not complete since in this latest case one SNP would be sufficient. Yet the problem of frequency above still remains with haplotypes instead of SNPs since the frequency of a haplotype cannot be higher than the highest SNP frequency involved.

#### *Statistical Methods to be used in Objective Analyses*

The statistical significance of the differences between variance frequencies can be assessed by a Pearson chi-squared test of homogeneity of proportions with  $n-1$  degrees of freedom. Then, in order to determine which variance(s) is(are) responsible for an eventual significance, we can consider each variance individually against the rest, up to  $n$  comparisons, each based on a  $2 \times 2$  table. This should result in chi-squared tests that are individually valid, but taking the most significant of these tests is a form of multiple testing. A Bonferroni's adjustment for multiple testing will thus be made to the P-values, such as  $p^* = 1 - (1-p)^n$ .

The statistical significance of the difference between genotype frequencies associated to every variance can be assessed by a Pearson chi-squared test of homogeneity of proportions with 2 degrees of freedom, using the same Bonferroni's adjustment as above.

Testing for unequal haplotype frequencies between cases and controls can be considered in the same framework as testing for unequal variance frequencies since a single variance can be considered as a haplotype of a single locus. The relevant likelihood ratio test compares a model where two separate sets of haplotype frequencies apply to the cases and controls, to one where the entire sample is characterized by a single common set of haplotype frequencies. This can be performed by repeated use of a computer program (Terwilliger and Ott, 1994, Handbook of Human Linkage Analysis, Baltimore, John Hopkins University Press) to successively obtain the log-likelihood corresponding to the set of haplotype frequency estimates on the cases ( $\ln L_{case}$ ), on the controls ( $\ln L_{control}$ ), and on the overall ( $\ln L_{combined}$ ). The test statistic  $2((\ln L_{case}) + (\ln L_{control}) - (\ln L_{combined}))$  is then chi-squared with  $r-1$  degrees of freedom (where  $r$  is the number of haplotypes).

To test for potentially confounding effects or effect-modifiers, such as sex, age, etc., logistic regression can be used with case-control status as the outcome variable, and genotypes and covariates (plus possible interactions) as predictor variables.

5

**Example 6****Exemplary Pharmacogenetic Analysis Steps**

In accordance with the discussion of distribution frequencies for variances, alleles, and haplotypes, variance detection, and correlation of variances or  
5 haplotypes with treatment response variability, the points below list major items which will typically be performed in an analysis of the pharmacogenetic determination of the effects of variances in the treatment of a disease and the selection/optimization of treatment.

- 10 1) List candidate gene/genes for a known genetic disease, and assign them to the respective metabolic pathways.
- 2) Determine their alleles, observed and expected frequencies, and their relative  
15 distributions among various ethnic groups, gender, both in the control and in the study (case) groups.
- 3) Measure the relevant clinical/phenotypic (biochemical / physiological) variables of the disease.
- 20 4) If the causal variance/allele in the candidate gene is unknown, then determine linkage disequilibria among variances of the candidate gene(s).
- 5) Divide the regions of the candidate genes into regions of high linkage  
25 disequilibrium and low disequilibrium.
- 6) Develop haplotypes among variances that show strong linkage disequilibrium using the computation methods.
- 7) Determine the presence of rare haplotypes experimentally. Confirm if the  
30 computationally determined rare haplotypes agree with the experimentally determined haplotypes.
- 8) If there is a disagreement between the experimentally determined haplotypes and  
35 the computationally derived haplotypes, drop the computationally derived rare haplotypes, construct cladograms from these haplotypes using the Templeton (1987) algorithm.

- 9) Note regions of high recombination. Divide regions of high recombination further to see patterns of linkage disequilibria.
- 10) Establish association between cladograms and clinical variables using the nested analysis of variance as presented by Templeton (1995), and assign causal variance to a specific haplotype.
- 11) For variances in the regions of high recombination, use permutation tests for establishing associations between variances and the phenotypic variables.
- 12) If two or more genes are found to affect a clinical variable determine the relative contribution of each of the genes or variances in relation to the clinical variable, using step-wise regression or discriminant function or principal component analysis.
- 13) Determine the relative magnitudes of the effects of any of the two variances on the clinical variable due to their genetic (additive, dominant or epistasis) interaction.
- 14) Using the frequency of an allele or haplotypes, as well as biochemical/clinical variables determined in the *in vitro* or *in vivo* studies, determine the effect of that gene or allele on the expression of the clinical variable, according to the measured genotype approach of Boerwinkle et al (Ann. Hum. Genet 1986).
- 15) Stratify ethnic/ clinical populations based on the presence or absence of a given allele or a haplotype.
- 16) Optimize drug dosages based on the frequency of alleles and haplotypes as well as their effects using the measured genotype approach as a guide.

### **Example 7**

#### **Exemplary Pharmacogenetic Analysis Steps - biological function analysis**

In many cases when a gene which may affect drug action is found to exhibit variances in the gene, RNA, or protein sequence, it is preferable to perform biological experiments to determine the biological impact of the variances on the structure and function of the gene or its expressed product and on drug action. Such experiments may be performed *in vitro* or *in vivo* using methods known in the art.

The points below list major items which may typically be performed in an analysis of the effects of variances in the treatment of a disease and the selection/optimization of treatment using biological studies to determine the structure and function of variant forms of a gene or its expressed product..

5 1) List candidate gene/genes for a known genetic disease, and assign them to the respective metabolic pathways.

10 2) Identify variances in the gene sequence, the expressed mRNA sequence or expressed protein sequence.

15 3) Match the position of variances to regions of the gene, mRNA, or protein with known biological functions. For example, specific sequences in the promotor of a gene are known to be responsible for determining the level of expression of the gene; specific sequences in the mRNA are known to be involved in the processing of nuclear mRNA into cytoplasmic mRNA including splicing and polyadenylation; and certain sequences in proteins are known to direct the trafficking of proteins to specific locations within a cell and to constitute active sites of biological functions including the binding of proteins to other biological constituents or catalytic functions. Variances in sites such as these, and others known in the art, are candidates for biological effects on drug action.

25 4) Model the effect of the variance on mRNA or protein structure. Computational methods for predicting the structure of mRNA are known and can be used to assess whether a specific variance is likely to cause a substantial change in the structure of mRNA. Computational methods can also be used to predict the structure of peptide sequences enabling predictions to be made concerning the potential impact of the variance on protein function. Most useful are structures of proteins determined by X-ray diffraction, NMR or other methods known in the art which provide the atomic structure of the protein. Computational methods can be used to consider the effect of changing an amino acid within such a structure to determine whether such a change would disrupt the structure and/or function of the protein. Those skilled in the art will recognize that this analysis can be performed on crystal structures of the protein known to have a variance as well as homologous proteins expressed from different loci in the human genome, or homologous proteins from other species, or non-homologous but analogous proteins with similar functions from humans or other species.

5) Produce the gene, mRNA or protein in amounts sufficient to experimentally characterize the structure and function of the gene, mRNA or protein. It will be apparent to those skilled in the art that by comparing the activity of two genes or their products which differ by a single variance, the effect of the variance can be determined. Methods for producing genes or gene products which differ by one or more bases for the purpose of experimental analysis are known in the art.

6) Experimental methods known in the art can be used to determine whether a specific variance alters the transcription of a gene and translation into a gene product. This involves producing amounts of the gene by molecular cloning sufficient for in vitro or in vivo studies. Methods for producing genes and gene products are known in the art and include cloning of segments of genetic material in prokaryotes or eukaryotic hosts, run off transcription and cell-free translation assays that can be performed in cell free extracts, transfection of DNA into cultured cells, introduction of genes into live animals or embryos by direct injection or using vehicles for gene delivery including transfection mixtures or viral vectors.

7) Experimental methods known in the art can be used to determine whether a specific variance alters the ability of a gene to be transcribed into RNA. For example, run off transcription assays can be performed in vitro or expression can be characterized in transfected cells or transgenic animals.

8) Experimental methods known in the art can be used to determine whether a specific variance alters the processing, stability, or translation of RNA into protein. For example, reticulocyte lysate assays can be used to study the production of protein in cell free systems, transfection assays can be designed to study the production of protein in cultured cells, and the production of gene products can be measured in transgenic animals.

9) Experimental methods known in the art can be used to determine whether a specific variant alters the activity of an expressed protein product. For example, protein can be produced by reticulocyte lysate systems or by introducing the gene into prokaryotic organisms such as bacteria or lower eukaryotic organisms such as yeast or fungus), or by introducing the gene into cultured cells or transgenic animals. Protein produced in such systems can be extracted or purified and subjected to bioassays known to those in the art as measures of the action of that particular protein. Bioassays may involve, but are not limited to, binding, inhibition, or catalytic functions.

10) Those skilled in the art will recognize that it is sometimes preferred to perform the above experiments in the presence of a specific drug to determine whether the drug has differential effects on the activity being measured. Alternatively, studies may be performed in the presence of an analogue or metabolite of the drug.

11) Using methods described above, specific variances which alter the biological function of a gene or its gene product that could have an impact on drug action can be identified. Such variances are then studied in clinical trial populations to determine whether the presence or absence of a specific variance correlates with observed clinical outcomes such as efficacy or toxicity.

12) It will be further recognized that there may be more than one variance within a gene that is capable of altering the biological function of the gene or gene product. These variances may exhibit similar, synergistic effects, or may have opposite effects on gene function. In such cases, it is necessary to consider the haplotype of the gene, namely the combination of variances that are present within a single allele, to assess the composite function of the gene or gene product.

13) Perform clinical trials with stratification of patients based on presence or absence of a given variance, allele or haplotype of a gene. Establish associations between observed drug responses such as toxicity, efficacy, drug response, or dose toleration and the presence or absence of a specific variance, allele, or haplotype.

14) Optimize drug dosage or drug usage based on the presence of the variant.

### **Example 8**

#### **Stratification of patients by genotype in prospective clinical trials.**

In a prospective clinical trial, patients will be stratified by genotype to determine whether the observed outcomes are different in patients having different genotypes. A critical issue is the design of such trials to assure that a sufficient number of patients are studied to observe genetic effects.

The number of patients required to achieve statistical significance in a conventional clinical trial is calculated from:

$$1.1 \quad N = 2(z_{\alpha} + z_{2\beta})^2 / (\delta/\sigma)^2 \text{ (two tailed test)}$$

From this equation it may be inferred that the size of a genetically defined subgroup  $N_i$  required to achieve statistical significance for an observed outcome associated with variance or haplotype "i" can be calculated as:

$$1.2 \quad N_i = 2(z_\alpha + z_{2\beta})^2 / (\delta_i / \sigma_i)^2$$

If  $P_i$  is the prevalence of the genotype "i" in the population, the total number of patients that need to be incorporated in a clinical trial  $N_g$  to identify a population with haplotype "i" of size  $N_i$  is given by:

$$1.3 \quad N_g = N_i / P_i$$

It should be noted that  $N_g$  describes the total number of patients that need to be genotyped in order to identify a subset of  $N_i$  patients with genotype "i".

If genotyping is used as means for statistical stratification of patients,  $N_g$  represents the number of patients that would need to be enrolled in a trial to achieve statistical significance for subgroup "i". If genotyping is used as a means for inclusion, it represents the number of patients that need to be screened to identify a population of  $N_i$  individuals for an appropriately powered clinical trial. Thus,  $N_g$  is a critical determinant of the scope of the clinical trial as well as  $N_i$ .

A clinical trial can also be designed to test associations for multiple genetic subgroups "j" defined by a single allele in which case:

$$1.4 \quad N_g = \max ( N_{gi} ) \text{ for } i=1 \dots j$$

If more than one subgroup is tested, but there is no overlap in the patients contained within the subgroups, these can be considered to be independent hypotheses and no multiple testing correction should be required. If consideration of more than one subgroup constitutes multiple testing, or if individual patients are included in multiple subgroups, then statistical corrections may be required in the values of  $z_\alpha$  or  $z_{2\beta}$  which would increase the number of patients required.

It should be emphasized that a clinical trial of this nature may not provide statistically significant data concerning associations with any genotype other than "i". The total number of patients that would be required in a clinical trial to test



more than one genetically defined subgroup would be determined by the maximum value of  $N_g$  for any single subgroup.

The power of pharmacogenomics to improve the efficiency of clinical trials arises from the fact it is possible to have  $N_g < N$ . The goal of pharmacogenomic analysis is to identify a genetically define subgroup in which the magnitude of the clinical response is greater and the variability in response is reduced. These observations correspond to an increase in the magnitude of the (mean) observed response  $\delta$  or a decrease the degree of variability  $\sigma$ . Since the value of  $N_i$  calculated in equation 1.2 decreases non-linearly as the square of these changes, the total number of patients  $N_g$  can also decrease non-linearly, resulting in a clinical trial that requires fewer patients to achieve statistical significance. If  $\delta_i$  and  $\sigma_i$  are not different than  $\delta$  and  $\sigma$ , then  $N_g$  is greater than  $N$  as given by  $N_g = N_i / P_i$ . Values of  $\delta_i$  and  $\sigma_i$  that give  $N_g < N$  can be calculated:

$$1.5 \quad N_g < N \text{ if: } P_i > [(\delta/\sigma)^2]/[(\delta_i/\sigma_i)^2]$$

It is apparent from this analysis that  $N_g$  is not uniformly less than  $N$ , even with modest improvements in the values for  $\delta_i$  and  $\sigma_i$ .

As with a conventional clinical trial, the incorporation of an appropriate control group in the study design is critical for achieving success. In the case of a prospective clinical trial, the control group commonly is selected on the basis of the same inclusion criteria as the treatment group, but is treated with placebo or a standard therapeutic regimen rather than the investigational drug. In the case of a study with subgroups that are defined by haplotype, the ideal control group for a treatment subgroup with hapotype "i" is a placebo-treated subgroup with haplotype "i". This is often a critical control, since haplotypes which may be associated with the response to treatment may also affect the natural course of the disease.

A critical issue in considering control groups is that  $\sigma$  for the control group placebo treated population with haplotype "i" may not be equivalent to that of the control population. If so, 1.5 may overestimate the benefits of any reduction in  $\sigma_i$  in the treatment response group if there is not also a reduction in  $\sigma_i$  in the control group.

If  $\sigma$  of the treatment and control groups are not equivalent,  $\delta$  would be still calculated as the difference in the response of the two groups, but  $\sigma$  would be

different in the two groups with values of  $\sigma_0$  or  $\sigma_1$  respectively. In this case, the number of patients in the genetically defined subgroup  $N_i$  would be defined by:

$$2.1 \quad N_i = (\sigma Z_{\alpha} + \sigma_i Z_{\beta})^2 / \delta^2$$

The total number of patients that would need to be enrolled in such a trial would be the maximum of

$$2.2 \quad N \text{ or } N/P_i$$

It will be apparent that such an analysis remains sensitive to increases in  $\delta$ , but is less sensitive to changes in  $\sigma$  which are not also reflected in the control group.

Certain analysis may be performed by comparing individuals with one haplotype against the entire normal population. Such an analysis may be used to establish the selectivity of the response associated with a specific haplotype. For example, it may be desirable to establish that the response or toxicity observed in a specific subgroup is greater than that associated observed with the entire population. It may also be of interest to compare the response to treatment between two different subgroups. If  $\sigma$  differs between the groups, then the estimate of the number of patients that need to be enrolled in the trial must be calculated using equations 2.1 with  $N$  being the maximum of  $N_i/P_i$  for the different subgroups.

Another issue in controls is the relative size of the treatment and control groups. In a prospectively designed clinical trial which selectively incorporates patients with haplotype "i" the number of patients in the control and treatment group will be essentially equivalent. If the control group is different, or if haplotypes are used for stratification but not inclusion, statistical corrections may need to be made for having populations of different size.

### **Example 9**

#### **Stratification of patients by phenotype.**

The identification of genetic associations in Phase II or retrospective studies can be performed by stratifying patients by phenotype and analyzing the distribution of genotypes/haplotypes in the separate populations. A particularly important aspect of this analysis is that any gene may have only a partial effect on the observed outcome, meaning that there will be an association value (A) corresponding to the

fraction of patients in a phenotypically-defined subgroup who exhibit that phenotype due to a specific genotype/phenotype.

It will be recognized to those skilled in the art that the fraction of individuals who exhibit a phenotype due to any specific allele will be less than 1 (i.e.  $A < 1$ ).

5 This is true for several reasons. The observed phenotype may occur by random chance. The observed phenotype may be associated with environmental influences, or the observed phenotype may be due to different genetic effects in different individuals. Furthermore, the construction of haplotypes and analysis of recombination may not group all alleles with phenotypically-significant variances within a single haplotype or haplotype cluster. In this case, causative variances at a single locus may be associated with more than one haplotype or haplotype cluster and the association constant  $A$  for the locus would be  $A = A_1 + A_2 + \dots + A_n < 1$ . It is likely that many phenotypes will be associated with multiple alleles at a given locus, and it is particularly important that statistical methods be sufficiently robust to identify association with a locus even if  $A_i$  is reduced by the presence of several causative alleles.

Statistical methods can be used to identify genetic effects on an observed outcome in patient groups stratified by phenotype, eg the presence or absence of the observed response. One such method entails determining the allele frequencies in two populations of patients stratified by an observed clinical outcome, for example efficacy or toxicity and performing a maximum likelihood analysis for the association between a given gene and the observed phenotype based on the allele frequencies and a range of values for  $A$  (the association constant between a specific allele and the observed outcome used to stratify patients).

25 This analysis is performed by comparing the observed gene frequencies in a patient population with an observed outcome to gene frequencies in a table in which the predicted frequencies of different alleles of the gene assuming different values of the association constant  $A$  for that allele. This table of predicted gene frequencies can be constructed by those skilled in the art based on the frequency of any specific allele in the normal population, the predicted inheritance of the effect (e.g. dominant or recessive) and the fraction of a subgroup with a specific outcome who would have that allele based on the association constant  $A$ .

For example, if a specific outcome was only observed in the presence of a specific allele of a gene, the expected frequency would be 1. If a specific outcome was never observed in the presence of a specific allele of a gene, the expected frequency would be 0. If there was no association between the allele and the observed outcome, the frequency of that allele among individuals with an observed outcome would be the same as in the general population. A statistical analysis can

be performed to compare the observed allele frequencies with the predicted allele frequencies and determine the best fit or maximum likelihood of the association. For example, a chi square analysis will determine whether the observed outcome is statistically similar to predicted outcomes calculated for different modes of inheritance and different potential values of A. P values can then be calculated to determine the likelihood that any specific association is statistically significant. A curve can be calculated based on different values of A, and the maximal likelihood of an association determined from the peak of such a curve. Methods for chi square analysis are known to those in the art.

A multidimensional analysis can also be performed to determine whether an observed outcome is associated with more than one allele at a specific genetic locus. An example of this analysis considering the potential effects of two different alleles of a single gene is shown. It will be apparent to those skilled in the art that this analysis can be extended to n dimensions using computer programs.

This analysis can be used to determine the maximum likelihood that one or more alleles at a given locus are associated with a specific clinical outcome.

It will be apparent to those skilled in the art that critical issues in this analysis include the fidelity of the phenotypic association and identification of a control group. In particular, it may be useful to perform an identical analysis in patients receiving a placebo to eliminate other forms of bias which may contribute to statistical errors.

### **Example 10**

#### **Amyotrophic Lateral Sclerosis**

##### ***I. Description of Amyotrophic Lateral Sclerosis***

Amyotrophic Lateral Sclerosis (ALS) is a degenerative neurological disease that primarily involves the motor neuron system. The disease is characterized by muscular atrophy, progressive weakness, fasciculations, spasticity, dysarthria, dysphagia, and respiratory compromise. Sensory, cognitive, oculomotor, and autonomic functions are spared. There are approximately 30,000 individuals with ALS in the U.S. with an estimated annual cost of \$300 million dollars. The majority of cases are sporadic and of unknown etiology, however approximately 5%-10% of ALS cases are inherited as an autosomal dominant trait (familial ALS). Superoxide dismutase 1 (SOD1) gene mutations are responsible for about 20% of familial ALS cases.

##### ***II. Current therapies for ALS***

There are no compounds that halt or prevent the progressive neurodegeneration of ALS. Riluzole (RILUTEK<sup>®</sup>), a benzothiazole derivative, is approved for treatment of ALS based on data that it slows disease progression and modestly increases survival time and ventilator-free time.. Riluzole's mechanism of action is not completely understood, however pharmacological properties include: 1) an inhibitory effect on glutamate release, 2) inactivation of voltage dependent sodium channels, 3) downmodulation of signalling via excitatory amino acid receptors, particularly glutamate receptors. Unfortunately riluzole, which was introduced in 1996, produces a benefit in only a fraction of patients, and the effect is modest. For example, despite the increase in longevity there is no consistent increase in muscular strength or pulmonary function. Thus patients do not experience significant relief from symptoms. Patients and care givers quickly understood these limitations, and consequently the use of the drug has been limited. A 1997 study, conducted during the first 8 months after commercialization of riluzole, found that only 37% of patients (17 of 46) eligible for riluzole were interested in trying the drug. The most common reason given for not wanting to try riluzole was insufficient benefit.

### III. *Limitations of Current Therapies for ALS*

As noted above, despite therapy with riluzole, in most ALS patients the disease progresses to debilitating and ultimately life-threatening symptoms. However, since there are no therapeutic alternatives, riluzole is frequently administered despite the modest efficacy. This practice increases the cost of ALS care significantly. In addition to unimpressive efficacy, riluzole therapy has been associated with elevation of serum ALT levels. Thus patients on riluzole should be monitored bimonthly for elevated liver enzymes, at significant cost. Other side effects, which occur infrequently, include neutropenia, asthenia, nausea, dizziness, decreased lung function, diarrhea, abdominal pain, pneumonia, vomiting, vertigo, paresthesia, anorexia, and somnolence. Attending to these iatrogenic effects further increases the costs associated with riluzin therapy.

### IV. *Potential Impact of Genotyping on Drug Development for ALS*

There is already a well established genetic cause of some familial ALS cases: mutation of the SOD-1 gene. It is likely that genetic factors play a role in the pathogenesis of sporadic ALS and non-SOD1 linked familial ALS. Strong candidate genes include, for example, other scavengers of superoxide, the entire glutamate signal transduction pathway, calcium channels and genes involved in the production and degradation of neurofilaments. Stratification of clinical trial patients

by allelic variation in these or other candidate genes may reveal differences in response rate, duration or quality of response, or adverse events that would be useful in the development of a compound. Provided in this invention are additional genetic pathways implicated in the disease process or response to candidate therapies.

5 Variation in these genes may account for the observed variability in treatment response. Exemplary variations in the candidate genes are provided in Tables 12-17 and 18-23. The Detailed Description above describes how one skilled in the art would identify a candidate gene or genes, identify sequence variances, stratify patients, design clinical trials, and obtain regulatory approval of a pharmacogenetic test for optimal responders to an ALS treatment. Gene pathways including most preferably, but not limited to, those genes that are listed in the gene pathway Table 2, and pathway matrix Table 7 and discussed in Section V. below are candidates for the genetic analysis and product development strategies described above.

#### 15 Advantages of Pharmacogenetic Clinical Development of Agents for ALS

In view of the limitations of present therapy, the advantages of an ALS clinical development program that includes genetic stratification of patients in the analysis of response to candidate therapeutic interventions are numerous. First, it may be possible to identify a subpopulation that responds to a treatment at a higher rate than the whole ALS population. This would address the demonstrated disinclination of ALS patients to expose themselves to therapies of limited effectiveness. It might also allow regulatory approval of therapies that do not produce a sufficient response in the unstratified population to justify approval. Second, it may be possible to identify patients who respond to a treatment only at higher doses than most patients require, or respond preferentially to an altered dosing route or schedule. Such customization of therapy to individual genetic and biochemical differences may allow a higher overall response rate to be achieved, without requiring totally empirical dose adjustment in each patient. Third, it may be possible to identify patients in whom side effects are likely to occur. Such patients could be offered alternative treatments. It is also worth noting that the type of benefit afforded by drugs such as RILUTEK® - a slowing of deterioration - will likely be most useful if the drug is started very early, before large numbers of neurons are gone. However the long term prophylactic use of medicines in well, or nearly well, individuals entails a different cost-benefit analysis than in already sick individuals. Identification of patients that respond well to early neuroprotective therapy may be aided by the analysis of genetic determinants of treatment response.

Additional uses of genetic stratification in clinical development have been described above.

As an example of a candidate gene with DNA sequence variances potentially relevant to drug efficacy, safety, or both consider the glutamate aspartate receptor NMDA 2C, a member of the glutamate pathway. Described in this application are novel NMDA 2C DNA sequence variances that the inventors have recognized may affect response to drugs. (Diseases in which the glutamate pathway is likely to play a role are summarized in Table 7) Six DNA sequence variances have been identified in the NMDA 2C gene, five of which alter the encoded amino acid sequence. Several of the amino acid variances are nonconservative, including phenylalanine-valine, glycine-arginine and arginine-serine (see Table 13 for details). Seven DNA sequence variances are described in the NMDA 2A receptor (Table 13). The effect of one or more of these genetic polymorphisms on efficacy or safety of an ALS treatment could be tested in a clinical trial. For example, the goal could be optimization of patient selection for glutamate channel antagonist therapy of ALS by determining whether an ALS patient has a NMDA 2A or 2C receptor genotype against which a glutamate antagonist is more effective or safer.

Similarly, for genes belonging to the other pathways relevant to treatment of ALS (see tables 2 and 7) and polymorphisms in those genes (tables 13 and 19) a strong argument can be made that said polymorphisms (or sets of polymorphisms, or haplotypes) may affect efficacy or safety of drugs active against ALS, including, but not limited to, drugs listed below in Table 25 and related compounds. The candidate genes include, but are not limited to, modulators of glutaminergic, serotonergic, GABAergic, melatonergic and opiate pathways, as well as calcium channels, cytokines, factors that mediate growth, differentiation and apoptosis, the coagulation cascade, second messenger systems, detoxification genes, particularly relating to superoxide, protein degradation and cytoskeleton genes.

#### *V. Therapeutic Strategies for ALS*

The etiology of most ALS cases is unknown but may involve autoimmune responses, for example to calcium channels, injury due to excessive excitotoxic stimulation (especially via aspartate, glutamate and GABA receptors), impaired clearance of free radicals, imbalance of neurofilament turnover or possibly viral mediated destruction of motor neurons (e.g. herpes virus). A number of drug development programs are aimed at these postulated pathophysiologic mechanisms. For example, there are candidate therapeutic agents that down modulate immune reactivity, block or dampen excitatory neurotransmitter signalling, alleviate free radical injury, and interfere with a hypothesized viral infection of motor neurons.

Beyond the specific mechanisms of action enumerated above, there are many compounds in development that are intended to halt, retard, or prevent neural cell degeneration, or promote neural cell regeneration. Many such compounds are in clinical development programs for multiple neurological diseases. For example, gabapentin is a compound with complex and incompletely understood pharmacology, but it shows anticonvulsant, antinociceptive, anxiolytic and neuroprotective activity in animal models. In ALS animal models gabapentin prevents neuronal death. One of its actions may be inhibition of glutamate synthesis by branched-chain amino acid aminotransferase (BCAA-t). Other compounds in development for ALS target proteins involved in growth control and differentiation, protein processing, intracellular second messenger cascades and cytoskeletal proteins (see 25 below for specific compounds and Table 1 for the candidate genes that may affect response to those compounds).

Below in Table 25 the therapies in development for ALS categorized by mechanism of action. The listed candidate therapeutic intervention response in patients with ALS may be affected by polymorphisms in genes as described above in the Detailed Description.

### **Example 11**

#### **Dementia**

##### *I. Description of Dementia*

Dementia is a general term for mental deterioration. clinical state characterized by a significant loss of function in multiple cognitive domains, not due to an impaired level of confusion. Diagnosis of dementia requires 1) assessment of an individual's current level of cognitive function with the ability to compare to past intellectual function, and 2) documenting a decline in intellectual function by serial examinations over time. A comprehensive, reliable, and universally accepted clinical classification of the clinical and neuropathological characteristics of senile dementia has been described. However, definitive diagnosis is obtainable only with pathological findings upon autopsy. Based upon these diagnoses, there are an estimated 4 million Americans with Alzheimer's disease (AD) and 10 million Americans with dementia of all types.

Besides AD, there are categories of dementia that include vascular dementia, lewy body disease, frontal lobe dementia, mixed dementia, and post-traumatic dementia. A number of different diseases or conditions are characterized by or involve loss of cholinergic function and/or defects in neuronal remodeling repair and may result in clinical symptoms of dementia. Among these are diseases such as Alzheimer's disease (AD), Huntington's disease, Parkinson's disease, and



amyotrophic lateral sclerosis (ALS). Dementia can further be a complication of the following: depression, drug intoxication, metabolic disorders, normal pressure hydrocephalus, subdural hematomas, and cerebrovascular insufficiency.

## II. *Current Therapies for Dementia*

Current therapies for the treatment of dementia include enhancement of cortical cholinergic function. In general, approaches to replacement of cholinergic function can be characterized as either: 1) therapies that compensate for existing damage; and 2) therapies that halt, retard, or prevent cerebral damage. Ideally, a therapy targeting both mechanisms could potentially reverse existing damage. There are two broad mechanisms to enhance cerebral cholinergic function; 1) to block metabolism of acetylcholine via an acetylcholinesterase inhibitor, or 2) agonists at muscarinic or nicotinic receptors.

Acetylcholinesterase inhibitors have recently been approved for the use in patients with mild to moderate Alzheimer's disease. These agents (donepezil, Tacrine) selectively inhibit the acetylcholinesterase enzyme and increases levels of cortical acetylcholine. In randomized controlled clinical trials, donepezil was shown to improve both cognitive performance and global functioning. The improvements are modest and may not be apparent until up to three months after commencement of treatment.

## III. *Limitations of Current Therapies for Dementia*

Despite the introduction of pharmacologic agents for the treatment of dementia, the mainstay of therapeutic management continues to be education, and support for caregivers, and treatment of complications. This is in part because the available acetylcholinesterase inhibitor (donepezil) has limited efficacy and has undesirable side effects. Thus, the clinician is faced with the dilemma of limited therapeutic alternatives and weighing the benefits against the side effects.

### Limitations of Acetylcholinesterase Therapy due to Low Efficacy

Acetylcholinesterase inhibitors have limited efficacy; only a fraction (modest improvement in 40-50%) of patients respond to therapy. The extent and progression of loss of cortical cholinergic neurons limit the therapeutic benefit of acetylcholinesterase inhibitors. Long-term benefit of inhibition of acetylcholinesterase activity is unproven. Further, there is no clinical evidence supporting the use of acetylcholinesterase inhibitors in the prevention of AD or in the treatment of more severe stages.

An additional efficacy concern of the acetylcholinesterase inhibitor is the latent period before demonstrable clinical benefit. In the same period there may be concurrent neurodegeneration. Thus, the clinician has limited therapeutic alternatives, the patient may have limited response to therapy, and the disease progresses. In many cases, medical management of dementia is reduced to treatment of complications or supportive care.

#### Limitation of Acetylcholinesterase Therapy due to Toxicity or Undesired Side Effects

Toxicities associated with the use of acetylcholinesterase inhibitors are 1) vagotonic effect on the myocardium resulting in bradycardia and complications of other myocardial syndromes, 2) gastrointestinal complications such as nausea, vomiting, diarrhea, 3) lowering of seizure threshold (since seizures can be a complication of AD, this side effect may be confused with the progression of the disease).

Other acetylcholinesterase inhibitors have been shown to have a severe hepatotoxic effect, those products have been removed from the market or clinical development programs.

#### *IV. Impact of Genotyping on Drug Development for Dementia*

As previously indicated, the pathways and genes emphasize the relationship with Alzheimer's disease. In connection with the development of Alzheimers, it had been found that the presence of the ApoE4 allele was associated with an earlier development of the disease than other alleles, and further was associated with a decreased response to present acetylcholinesterase inhibitors, such as tacrine. The  $\epsilon 4$  allele of Apolipoprotein E (ApoE) is a well-established risk factor for late onset Alzheimer's disease. The work of Poirier (1995) and Farlow (1998) suggests there are significant interactions between sex, ApoE genotype, and therapeutic response (ADAS-Cog scores) to the acetylcholinesterase inhibitor tacrine, with the  $\epsilon 4$  allele generally associated with poor response and the effect being more notable in women than in men. ApoE is only part of the brain lipid transport pathway, however, and the interaction of allelic variation at other components of this pathway with drug response can also contribute to variation in therapeutic responses.

Sequence variance in the butyrylcholinesterase (BCHE) gene has been found to correlate with the development of Alzheimer's disease, as well as with treatment efficacy of both cholinomimetic and non-cholinomimetic drug therapies. In this case, the presence of at least one BCHE-k allele is predictive of the development of

Alzheimer's disease and is negatively correlated with treatment efficacy of tacrine (a cholinesterase inhibitor) and an experimental vasopressinergic drug (a non-cholinomimetic drug). The BCHE-k allele has a point mutation at nucleotide 1828 (a G to A substitution) which results in an ala539thr change. This polymorphism can  
5 be readily detected by PCR amplifying a region surrounding the variance site and sequencing the amplification product to determine the nucleotide at the particular site.

A group of patients was treated with an experimental vasopressinergic drug (n = 91) and compared to patients administered a placebo (n = 108) without  
10 segregation or stratification by BCHE or other allelic status. As evaluated using the Mini Mental State Examination (MMSE) over a twelve-week treatment period, no statistically significant improvement was shown for the treatment group. However, when the treatment group was stratified according to the presence or absence of a BCHE-k allele, those patients without such an allele showed a statistically  
15 significant improvement while those having at least one of the BCHE-k alleles did not. Thus, the analysis provides an example of a gene where a patient sub-population was identified where a treatment showed a positive response even though no such positive response was found for the overall patient population. Indeed, those patients not having a k-allele are approximately three times more likely to  
20 respond to the vasopressinergic drug than are patients having at least one k-allele.

The response of Alzheimer's disease patients treated with the cholinomimetic drug, tacrine, was also determined. Similar to the above, the MMSE test was utilized as an indicator of a positive response. The positive response rate was approximately two-fold higher in those patients not having a k-  
25 allele than in those patients having at least one k-allele.

In addition, it was found that the presence of either or both of a BCHE-k allele and an apoE-4 allele was positively correlated with the development of Alzheimer's disease. For example, in patients over 75 years of age, the odds ratio of a patient having a BCHE-k allele was 2.3, the odds ratio for having a apoE-4 allele  
30 was 2.0, and the odds ratio for the joint occurrence of both alleles was 17.5. Thus, the BCHE-k allele is an example where the presence of a variant allele is negatively correlated with the efficacy of treatment with drugs from multiple drug categories, and which is further positively correlated with the development of a particular disease. Thus, the variance status of such a gene is useful both as a prognostic tool  
35 for disease risk, as well as for identifying likely drug responders versus non-responders for drug development and/or treatment selection.

The evidence that a variance in a gene involved in a pathway that affects drug response in patients with dementia, indicates and supports the theory that there

is a likelihood that other genes have similar qualities to various degrees. As drug research and development proceeds to identify more lead candidate therapeutic interventions for dementia, there is possible utility in stratifying patients based upon their genotype for these yet to be correlated variances. Further, as described in the Detailed Description, methods for the identification of candidate genes and gene pathways, stratification, clinical trial design, and implementation of genotyping for appropriate medical management of a given disease is easily translated for dementia. As described below in section V. below there are likely gene pathways as are those that are outlined in the gene pathway Table 2 and matrix Table 7.

#### Advantages of Pharmacogenomic Clinical Development of Therapies for Dementia

The advantages of a clinical research and drug development program that includes the use of polymorphic genotyping for the stratification of patients for the appropriate selection of candidate therapeutic intervention includes 1) identification of patients that may respond earlier to therapy, 2) identification of the primary gene and relevant polymorphic variance that directly affects efficacy, safety, or both, 3) identification of pathophysiologic relevant variance or variances and potential therapies affecting those allelic genotypes or haplotypes, and 4) identification of allelic variances or haplotypes in genes that indirectly affects efficacy, safety or both.

Based upon these advantages, designing and performing a clinical trial, either prospective or retrospective, which includes a genotype stratification arm will incorporate analysis of clinical outcomes and genetic variation associated with those outcomes, and hypothesis testing of the statistically relevant correlation of the genotypic stratification and therapeutic benefits. If statistical relevance is detectable, these studies will be incorporated into regulatory filings. Ultimately, these clinical trial data will be considered during the approval for marketing process, as well as, incorporated into accepted medical management of dementia.

By identifying subsets of patients with mild to moderate dementia that respond earlier to drugs or agents or experience enhanced efficacy, optimal candidate therapeutic interventions may reduce the period of time prior to relief of cognitive impairments. Appropriate genotyping and correlation to dosing regimen would be beneficial to the patient, caregivers, medical personnel, and the patient's loved ones.

Optimization of cholinomimetic mediated therapy of dementia further demonstrates the utility of selection of a potential dementia patient that has a predisposing genotype in which selective cholinomimetic are more effective and or are more safe. In considering an optimization protocol, one could potentially

predetermine variance or variances within the muscarinic cholinergic receptor, nicotinic cholinergic receptor, modulatory mechanisms of cholinergic neurotransmission, or cholinergic receptor mediated intracellular mechanism of action that is preeminently responsible for drug response. By embarking on the previously described gene pathway approach, it is technically feasible to determine the relevant genes within such a targeted drug development program for dementia.

*V. Description of Mechanism of Action Hypotheses for Future Drug Development for the Therapy of Dementia*

Drug development programs for the identification of novel drug or candidate therapeutic interventions are aimed at the underlying pathophysiologic mechanisms of the disease leading to clinical signs and symptoms of dementia. Current hypotheses include, but are not limited to, therapeutic development in one of the following areas: 1) replacement of cholinergic function, 2) acetylcholine pathway: biosynthesis, secretion, degradation, reuptake, and receptor binding, 3) CNS lipid transport/membrane repair pathway and gene identification, 4) inflammatory mediators, e.g. prostaglandin, prostacylin, and thromboxane pathway, and 5) constituents of AD lesions and AD genes. These are described in detail below.

A. Therapeutic Approaches for Replacement of Cholinergic Function

Because dementia is apparently related to a loss of cholinergic function in the neocortex and forebrain arising from death or atrophy of basal forebrain cholinergic neurons, replacement of cholinergic function has been shown to have therapeutic benefit. In general, novel approaches for the replacement of cholinergic function can be characterized as either: 1) therapies that compensate for existing damage; and 2) therapies that halt, retard, or prevent cerebral damage.

B. Therapeutic approaches that compensate for existing damage

The therapeutic approaches that may compensate for existing damage include modulating cholinergic deficit, modulating other neurotransmitter deficits, modulating immune or inflammatory mechanisms of neural damage, and modulation of metabolism of specific neurotransmitters. Although these novel therapies are aimed at existing or damage yet to occur, the underlying course of the disease will remain.

Potential therapies for the compensation for cholinergic deficit are 1) increase presynaptic production of acetylcholine, 2) enhance release of acetylcholine, 3) stimulate choline reuptake, 4) selective muscarinic agonists, 5)

anticholinesterase inhibitors, 6) mixed action anticholinesterases and muscarinic receptor ligands, and 6) nicotinic receptor agonists.

Potential therapies for the compensation for modulating other neurotransmitters are 1) selective NMDA agonists, and 2) other disorders of neurotransmitter function.

Potential therapies for the compensation for modulating immune or inflammatory mechanisms of neural damage are 1) antiinflammatory agents that suppress inflammation and 2) inhibition of amyloid precursor protein (APP) degradation.

Potential therapies that compensate for monoamine metabolite deficits are agents that affect monoamine oxidase type B enzyme activity, therapy for behavioral symptoms of neurotransmitter function in dementia, and compensate for immune or inflammatory mechanisms involved in neural cell destruction.

#### C. Therapeutic approaches that halt, retard, or prevent cerebral damage

In general therapeutic approaches that halt, retard, or prevent cerebral neural damage are currently either growth factors or modulation of the deposition of aberrant pathological depositions of metabolic by-products. These approaches include promotion of the growth and regeneration of cholinergic neurons and generally include growth factors that act on neurons, neural precursors, or glial cells. Growth factors include but are not limited to nerve growth factor (NGF), brain-derived growth factor (BDGF), neurotrophins, and leukemia inhibitory factor (LIF).

Prevention of amyloid plaque deposition includes modulation of APP gene expression, prevention of the development of amyloidogenic peptide, inhibition of amyloid aggregation/secretion, and APP antagonists. Prevention of the formation of neurofibrillary tangles includes modulation of the phosphorylation of tau proteins.

#### D. CNS Lipid Transport/Membrane Repair Pathway and Gene Identification

Brain Apolipoproteins: The six apolipoproteins known to be expressed in the brain are listed below. They are present on the surface of three major types of lipoproteins, one class enriched in A-I, but also containing most of the D,E, and J protein in the brain; one class composed principally of E with minor amounts of A-I, A-IV, D, and J; and a third minor class containing the majority of A-IV. Variation in the structure or expression of these apolipoproteins can modulate lipid transport and brain remodeling.

Lipoprotein Receptors: Six brain receptors for lipoproteins have been identified in man. These include the low density lipoprotein receptor (LDL-R), the LDL receptor-related protein (LRP), the very low density lipoprotein receptor

(VLDL-R), and the class A macrophage scavenger receptor, all of which are also expressed outside the brain. Two new protein with LDL receptor-like domains have recently been identified in human brain: Apolipoprotein E receptor type 2, and the SorLA-1 receptor. Alterations in the structure or expression of those receptors can affect binding of ApoE alleles (ApoE2, for example, has reduced affinity for the LDL receptor), and more generally will modulate the biology of lipid transport.

Lipoprotein docking and lipid mobilization: Heparin sulfate proteoglyans (HSPG) are responsible for initial binding of ApoE-bearing lipoproteins to cells. Removal of HSPGs with heparinase blocks binding, even in the presence of receptor (LDL-R or LRP). Therefore variations in biosynthetic enzymes of the HSPG pathway will influence lipoprotein uptake. Lipid hydrolysis by cholesterol ester transfer protein (CETP) effects the transport of lipids from lipoproteins into cells.

Cholesterol Metabolism: Acyl CoA:cholesterol acyltransferase and HMG CoA reductase are responsible for the metabolism of cholesterol, therefore variations in the metabolic pathway of cholesterol will influence availability of cholesterol.

Hormonal control of lipoproteins and lipoprotein receptors: The expression of lipoproteins and their receptors is under hormonal control. Clinical studies of tacrine for Alzheimer's disease have also shown reduced incidence of AD in women taking estrogen supplements post menopausally. Therefore, variation in hormone levels, hormone receptors, or hormone receptor signaling pathways will modulate response to acetylcholinesterase inhibitors, e.g., by affecting lipid transport and cholinergic remodeling or by other means. Hormone receptors that bind their physiologic ligand within the cytoplasm then become activated and cross the nuclear membrane include but are not limited to growth hormone, prolactin, estrogen, retinoic acid receptor, thyrotropin releasing hormone. Associated transcriptional co-activators include but are not limited to SRC-1, SRC-2 (TIF-2), SRC-3 (p/CIP:AIB1), P/CAF, CBP, E6-AP, TRIP230, SMRT, SRA, and N-CoR.

#### E. Prostaglandin, Prostacyclin, and Thromboxane Pathway

Inflammatory mediators, and in particular the products of arachidonic acid metabolism, play a role in the development of AD neuropathology.

There are several lines of evidence supporting the role of inflammatory or immunological processes in the pathogenesis of Alzheimer's disease. First, neurodegeneration in AD is accompanied by manifestations of immune reaction including activation of the complement cascade, accumulation and activation of microglia and presence of inflammatory cytokines and acute phase reactants in tissue of AD brains. Second, epidemiological studies suggest that use of non-steroidal anti-inflammatory drugs (NSAIDs) delays the clinical expression of

Alzheimer's disease. The development of selective COX inhibitors has led to renewed interest in the therapeutic potential of NSAIDs in AD.

Arachidonic acid formation pathway genes include phospholipase A2, phospholipase C  $\beta$ 3, and diacylglycerol lipase. PGG2 formation pathway genes include cyclooxygenase I, cyclooxygenase II. PGH2 formation pathway genes include PGG2 reductase. PGH2 metabolizing enzymes include PGH2 reductase, PGD2 reductase, PGH-PGE isomerase, and thromboxane A2 synthase. Receptors include PGF1a receptor, PGD2 receptor, PGE2 receptor, PG12 receptor, and thromboxane A receptor. Exemplary variances for genes above are shown in Tables 13 and 19.

#### F. Constituents of Alzheimer's Disease Lesions and AD Genes

The relative contribution of different pathogenetic mechanisms to the development of AD in specific patients can affect the degree of cholinergic impairment and hence the response to acetylcholinesterase inhibitors.

There is clear evidence that different pathogenetic mechanisms affect the onset and rate of progression of AD. The possible effects of such are several lines of evidence supporting the role of inflammatory or immunological processes in the pathogenesis of Alzheimer's disease. First, neurodegeneration in AD is accompanied by manifestations of immune reaction including activation of the complement cascade, accumulation and activation of microglia and presence of inflammatory cytokines and acute phase reactants in tissue of AD brains. Second, epidemiological studies suggest that use of non-steroidal anti-inflammatory drugs (NSAIDs) delays the clinical expression of Alzheimer's disease. The development of selective COX inhibitors has led to renewed interest in the therapeutic potential of NSAIDs in AD. Pathway genes include Tau protein, amyloid precursor protein, presenilin 1, and presenilin 2.

In Tables 13 and 19, there are listings of candidate genes and specific single nucleotide polymorphisms that may be critical for the identification and stratification of a patient population diagnosed with dementia based upon genotype. Current pathways that may have involvement in the therapeutic benefit of dementia include, but are not limited to, glutaminergic, serotonergic, dopaminergic, adrenergic, cholinergic, histaminergic, purinergic, GABAergic, glycinergic, nitric oxide, peptide protein processing, opiates, cholecystokinin, corticotropin releasing factor, thyroid stimulating hormone, somatostatin, adrenocorticotrophic hormone, vasoactive intestinal peptide, calcium or potassium channels, prostaglandin, cytokines, estrogen, clot formation, hemostasis, oxygenstress, mitochondrial



5 maintenance, protein maturation and degradation, second messenger cascade, growth, differentiation and apoptosis, cytoskeleton, secretion, amyloid processing, and lipid transport or metabolism gene pathways that are listed in Tables 1-6, 12-17 and 18-23. One skilled in the art would be able to identify these pathway specific gene or genes that may be involved in the manifestation of dementia, are likely candidate targets for novel therapeutic approaches, or are involved in mediating patient population differences in drug response to therapies for dementia.

10 A sample of therapies approved or in development for preventing or treating the progression of symptoms of dementia currently known in the art is shown in Table 27. In this table, the candidate therapeutics were sorted and listed by mechanism of action. Further, the product name, the pharmacologic mechanism of action, chemical name (if specified), and the indication is listed as well.

15 Based upon these varying approaches there are many products in development for dementia. In Table 27 below lists current therapies that are in development for U.S. marketing approval. Identification of genes in specific pathways and the link to specific agents or drugs may be useful to conduct clinical trials and achieve higher degrees of safety and efficacy. The listed candidate therapeutic interventions response in patients with dementia may be affected by polymorphisms in genes as described above.

## 20 **Example 12**

### Depression

#### *I. Description of Depression*

25 Major depression is a psychiatric disorder distinguishable from normal grief, sadness, and disappointment as well as the dysphoria and demoralization often associated with medical illness. Depressive disorders are characterized by abnormally long term depressed mood and may be accompanied by delusions and hallucinations. Individuals suffering from depression have feelings of despair and intense sadness, exhibit mental slowing and loss of concentration, are preoccupied with pessimistic worry and inner self, and are agitated and tend toward self-deprecation. In some depressive disorders, mania is present usually in episodic intervals and in these cases depressed mood is replaced with feelings of grandiosity and may be accompanied by incoherent speech. Clinically, unipolar or bipolar depression are terms used to describe the two broad categories of depressive disorders characterized by the absence or presence of episodic mania, respectively.

#### 35 *II. Current Medical Management Strategies for Depression*

### Unipolar Depression

Depression is a wide-spread disease that requires improved therapeutic alternatives to the conventional agents that have been available since the 1960s. Current therapeutic candidates of unipolar or bipolar depression are as follows:

5 tricyclic antidepressants, tetracyclic antidepressants, lithium, monoamine oxidase (MAO) inhibitors, electroconvulsive therapy (ECT) and atypical agents such as PROZAC<sup>®</sup>, WELLBUTRIN<sup>®</sup>, and trazodone.

### Bipolar Depression

10 Despite the difficulties of medical management of bipolar depression, advances have changed therapeutic outcomes. Therapies such as lithium, valproate, and carbamazepine, clozapine, and ECT have made a positive impact on the patient outcomes. Further, the importance of psychosocial issues for understanding patients illnesses and factors affecting treatment compliance are more fully realized.

15 For bipolar depression, mood stabilizers are the first line therapy and include: lithium, valproate, and carbamazepine. Adjunct therapies are used for the treatment of agitation, insomnia, or aggressive behaviors and include benzodiazepines and antipsychotics. ECT is useful as an alternative therapy in patients who are pregnant or are trying to conceive, unresponsive to standard therapy, unable to tolerate first line therapies, or are refractory to first line or adjunct therapies. ECT has been shown to be effective as stated above, as well as 54% effective in refractory patients.

20

There are additional therapies that have been used for the treatment of bipolar depression. For example, off-label use of clozapine, Ca<sup>++</sup> channel antagonists, gabapentin, and lamotrigine in diagnosed bipolar patients have been demonstrated to be effective at stabilizing mood. Gabapentin, has a higher safety profile during pregnancy, but has side effects of ataxia, fatigue and somnolence. Lamotrigine, by effectively lowering glutamine release is effective at stabilizing mood, but is associated with dizziness, headache, double vision, somnolence, headache, and rash. Other medications include valproate for euphoric mania, valproate for dysphoric mania or mixed mania, and clozapine with lithium or valproate for patients with rapid-cycling episodes.

25

30

### *III. Limitation of Current Therapies for Depression*

35 Frequently, depression is undiagnosed and if detected, treatment often is inadequate. Therapy of depression is associated with undesirable side effects and/or simply fails to adequately manage the symptoms of the condition. Thus, there is a

need for ongoing improved development of antidepressant therapeutic alternatives to the currently available products.

#### Limitations of Current Therapies for Unipolar Depression

Although these agents or therapies are efficacious (e.g. 80% improvement following ECT; lithium effectively prevents relapses in 60% of patients) there are significant limitations to their use and are 1) the onset of action of antidepressant drugs is latent, 2) responsivity and efficacy is not uniform, 3) long-term treatment can lead to symptoms of drug resistance, 4) there is perceived inhibition of creativity and decreased energy, and 5) there are patients with refractory depression with no therapeutic alternatives.

#### Limitations of Current Therapies for Bipolar Depression

Bipolar depression patients have additional therapeutic concerns as compared to unipolar depression patients. For bipolar patients there is the added difficulty of treating depression episodes. The efficacy of antidepressants is not well founded or documented in bipolar depression. Further, antidepressants have been documented to induce manic or hypomanic symptoms. Therefore, mood stabilizers are the first line therapy with adjunct therapies during manic or depression episodes.

An additional therapeutic issue associated with bipolar patients is that many comorbid psychiatric disorders occur within the same patient not only hindering a diagnosis, but also therapy. For example, substance abuse disorders, panic disorders, obsessive-compulsive disorders, and impulsive control disorders are often present and potentially mask symptoms of bipolar depression.

#### *IV. Impact of Pharmacogenomics on Drug Development for Depression*

There are two genes that have been described having polymorphisms that affect antidepressant drug response, the serotonin transporter gene and the angiotensin converting enzyme that affects the metabolism of substance P. These two examples are described below.

##### The Serotonin Transporter Gene

The serotonin transporter gene (5-HTT) polymorphism provides an example of a recessive SNP polymorphism in the non-coding region with an impact on inefficacy of a 5-HTT selective drug.

The serotonin transporter (5-HTT) plays a critical role in the termination of the serotonin (5-HT) neurotransmission and represent the prime target for selective

serotonin reuptake inhibitors (SSRIs). A functional polymorphism in the transcriptional control region upstream of the 5-HTT coding sequence has been reported. It consists of a 44 –base pair insertion (long variant) or deletion (short variant). It has been demonstrated that the long (l) and short (s) variants of this 5-HTT gene-linked polymorphic region had different transcriptional efficiencies. *In vitro* studies showed that the difference in 5-HTT mRNA synthesis result in different 5-HTT expression and 5-HT cellular uptake (Lesch et al. Science 1996 274:1527-153). Recently, it has been shown that an SSRI (fluvoxamine) efficacy in delusional depression seems to be related to allelic variation within the promoter of the 5-HTT gene (Smeraldi et al. Mol. Psychiatry 1998; 3:508-511). Both homozygotes for the long variant (l/l) of the 5-HTT promoter and heterozygotes (l/s) showed a better response to fluvoxamine than homozygotes for the short variant (s/s). Interestingly, the addition of pindolol (a mixed adrenoreceptor and 5-HT1A antagonist) has been proposed as an augmentation therapy for non-responders or partial responders to SSRIs, and it appears that in the group treated with fluvoxamine plus pindolol all the genotypes acted like l/l treated with fluvoxamine alone. This supports the hypothesis that the effect of pindolol is related to its ability to block 5-HT1A autoreceptors, thus preventing a negative feed-back of 5-HT at somatodendritic level. Furthermore, the activation of 5-HT1A autoreceptors could modulate the clinical effect of the SSRIs-induced 5-HTT blockade.

The 5-HTT polymorphism represents an example of a gene allelic variance that affects the transcriptional control, and ultimately, the amount of available transporter protein. In these cases, the gene product concentration or protein availability affects the function of the native mechanism and ultimately the ability of the drug to intervene with physiological function. One skilled in the art, upon utilizing the techniques described in the detailed description, would be able to identify known variances within a candidate gene, provide a diagnostic test to identify individuals with that variance or variances, group the individuals based upon the identified genotype, and design and implement a clinical study to test the effect a candidate drug has on the the groups. In this example, the allelic differences may affect transcriptional or translational control of the 5-HTT gene. A skilled practitioner will be able to utilize the techniques known in the art to determine the effects of a variance or variances within a gene promoter region to be able to study the impact those allelic differences have on the safety or efficacy of SSRIs or any other candidate drugs affecting the 5-HT pathway. Further, this example underscores the ability of a skilled practitioner to be able to utilize methods known in the art to design a pharmacogenomics clinical trial when the allelic difference is within the gene promoter region.

### The Angiotensin Converting Enzyme Gene and Substance P

The localization of substance P in brain regions that coordinate stress responses and receive convergent monoaminergic innervation suggested that substance P antagonists might have psychotherapeutic properties. Similar to clinically used antidepressant and anxiolytic drugs, substance P antagonists suppress isolation-induced vocalizations in guinea pigs. In a placebo-controlled trial in patients with moderate to severe major depression, robust antidepressant effects of the substance P antagonist MK-869 were consistently observed. In preclinical studies, substance P antagonists did not interact with monoamine systems in the manner seen with established antidepressant drugs. These findings suggest that substance P may play an important role in psychiatric disorders.

Substance P is highly metabolized by ACE (angiotensin converting enzyme) which is a good actual example of pharmacogenetics: It has a high allele frequency in normal individuals (D: 34%, I: 66%) and there are clinical studies clearly demonstrating its impact on ACE inhibitors.

Moreover, it has been shown that DD homozygous patients (11%) have a higher brain level of substance P than II homozygous patients (43%), with an intermediate level for heterozygous patients (46%).

Using results of the initial phase II trial, we expect that a substance P antagonist will have more impact on patients with high brain level of substance P (actually, the DD patients who are more at risk for affective disorders). As measure of response rate, starting with the standard measure of response defined as  $\geq 50\%$  change from baseline to week 6 in total HAM-D21 score, 54% of the patients improved with MK-869 and 28% patients improved with placebo in the phase II trial.

In a recent clinical trial of MK-869 versus placebo, a similar response rate was observed for both groups (54% and 48% respectively). If the ACE variance is considered as a dominant SNP with regard to substance P metabolism, calculation of an unequivocal positive response rate in the DD subgroup (i.e., 100%) would require an equally similar response rate in the II subgroup, while assuming the DI subgroup response rate remains similar to placebo (i.e., 48%). In this case, MK-869 would be positive (100%) only in a fraction of the patients, e.g., one out of every five.

Approximately 25% of the responders should be DD homozygous; if not, the hypothesis is not valid. Then, if 25% are DD, the number of patients included in the failed trial should be enough to see a statistically significant difference between the DD subgroup and other patients, since we would need at least 56 patients to test for such a high relative risk ( $100\% / 48\% = 2$ ).

This approach exemplifies the utility of high allele frequency polymorphisms. Further, when the treatment is not efficacious for all individuals (i.e. response rates vary between treatment groups is less than 15%) the allele frequency of a potentially interacting recessive SNP polymorphism should be relatively high (e.g. from 30% for a 15% difference in response rate to 60%). This corresponds to 16% or less of total patients (see example 18 and table below).

The evidence that a variance in a gene involved in a pathway affects antidepressive drug response, indicates and supports the idea that other genes have similar qualities to various degrees. As drug research and development proceeds to identify more lead candidate therapeutic interventions for depression, there is utility in stratifying patients based upon their genotype for these yet to be correlated variances. Further, as described in the Detailed Description, methods for the identification of candidate genes and gene pathways, stratification, clinical trial design, and implementation of genotyping for appropriate medical management of a given disease is easily utilized for depression. As described below in section V, below there are likely gene pathways such as those outlined in the gene pathway Table 2 and matrix Table 7.

Optimization of adrenergic control or ion channel modulation mediated therapy of epilepsy further demonstrates the utility of selection of a potential epilepsy patient that has a predisposing genotype in which selective adrenergic or agents are more effective and or are safer. In considering an optimization protocol, one can potentially predetermine variance or variances within the adrenergic receptor, ion channel or ion channel mediated mechanisms of neurotransmission, or adrenergic receptor mediated intracellular mechanism of action that is preeminently responsible for drug response. By embarking on the previously described gene pathway approach, it is technically feasible to determine the relevant genes within such a targeted drug development program for depression.

A sample of therapies in development for preventing or treating the progression of symptoms of depression currently known in the art is shown in table 28. In this table, the candidate therapeutics were sorted and listed by mechanism of action. Further, the product name, the pharmacologic mechanism of action, chemical name (if specified), and the indication is listed as well.

#### *V. Mechanism of Action Hypotheses for Novel Therapies for Depression: Utility of Genotyping*

##### Unipolar Depression

Unfortunately, to date the biological mechanism of major unipolar depression is unclear. However, studies of endocrine systems, neurotransmission, and neuroelectrophysiology have provided the basis for the generation of pathophysiologic hypotheses. These hypotheses have been supported by clinical data stemming from the success of conventional treatment of depression.

One such hypothesis is that there is pituitary-hypothalamic dysfunction in depressed patients. It has been observed that depressed patients commonly have elevated levels of cortical steroids in their urine and blood. Further, 50% of the patients with clinical depression will not secrete cortisol when subjected to the dexamethasone suppression test. Additionally, thyrotropin releasing hormone (TRH) stimulation of thyrotropin stimulating hormone (TSH) release is aberrant in depressed patients without an alteration of serum T3 or T4 concentrations and growth hormone, prolactin, gonadal hormones, corticotropin releasing factor (CRF), and melatonin have diminished physiologic responses.

Another hypothesis of the biological dysfunction of depression is that there is a neurotransmitter dysfunction due to a catecholamine-indolamine imbalance. This theory postulates that there is a required level of catecholamines and receptor sensitivity required for normal mood. In depression, there may be aberrant receptor insensitivity, depletion of amines, or a depletion of their synthesis or storage that leads to depression. Supporting this theory is that monoamine oxidase inhibitors increase the availability of catecholamines and indolamines and have been used clinically for the management of depression.

The cholinergic neurotransmitter system has been implicated in the manifestation of depression. It has been postulated that there is an imbalance of adrenergic and cholinergic control of neural transmission in patients with depression.

Electrophysiologic studies have shown that patients with depression have altered rapid eye movement (REM) sleep patterns, i.e. shortened REM latency, than non-depressed patients. Other studies have documented a correlation of the circadian rhythm and precipitation of depressive episodes during autumn and winter months and diminished ambient light during those times during the year.

In each of the theories posited and described above, satisfactory conclusions are limited. Conventional therapy of depression with tricyclic antidepressants has demonstrated that this treatment affects more than one neurotransmitter system due to either modification or alteration of the regulation of neurotransmitter receptors signaling pathways rather than acting solely at neurotransmitter receptor binding.

Novel therapies of unipolar depression include venlafaxine and mirtazapine. Both of these compounds show promise in clinical trials for the treatment of

depression. Venlafaxine is a mixed serotonergic and noradrenergic reuptake inhibitor. Mirtazapine has noradrenergic and serotonergic antidepressant mechanism of action. These two products have what looks to be superior action over tricyclic antidepressants or selective serotonergic inhibitors (SSRIs).

### Bipolar Depression

Theories for the mechanism have been described. In one model, electrophysiological kindling and behavior sensitization underlie bipolar disorders and further increasing frequencies of episodes over time. In another model, there appears to be a desynchronization of circadian rhythm in bipolar patients.

As for depression, the catecholamine hypothesis presumes that mania is due to an excess of catecholamines and depression is due to their depletion. Noradrenergic and dopaminergic dysfunction have both been linked to depression. In both cases of dysfunction, there appears to be causal links, i.e. aberrant noradrenergic neurotransmission and L-dopa induced hypomania among bipolar patients, respectively. Amphetamines can produce hypomania in bipolar patients and dopaminergic antagonists are effective for severe mania.

The serotonergic hypothesis generalizes that low serotonergic transmission is responsible for mania and depression because low serotonergic inputs may result in defective neuromodulation. Other hypotheses include neurotransmitters, enzymes, neuropeptides, and theories involving endocrine and immunological systems. As in many other complex disorders of psychological function, these models fall short of adequately describing the disturbance. Future studies and drug development may provide insights to refined biological mechanism of bipolar depression.

In Tables 13, and 19, there are listings of candidate genes and specific single nucleotide polymorphisms that may be critical for the identification and stratification of a patient population diagnosed with depression based upon genotype. Current pathways that may have involvement in the therapeutic benefit of depression include glutaminergic, serotonergic, dopaminergic, adrenergic, cholinergic, purinergic, GABAergic, melatonin, peptide protein processing, opiates, oxytocin, neuropeptide Y, calcitonin/calcitonin gene related peptide, tachykinin, corticotropin releasing factor, vasopressin, calcium or potassium channels, prostaglandin, testosterone, oxygen stress, second messenger cascade, folate metabolism pathways that are listed in Tables 2, 7, 13, and 19. One skilled in the art would be able to identify these pathway specific gene or genes that may be involved in the manifestation of depression, are likely candidate targets for novel therapeutic approaches, or are involved in mediating patient population differences in drug response to therapies for depression.



In Table 28 below is a list of the available candidate therapeutic alternatives available or in development for depression. There are listed by therapeutic approach are defined and listed in Table 2. The listed candidate therapeutic interventions response in patients with depression may be affected by polymorphisms in genes as described above.

### **Example 13**

#### **Epilepsy**

##### *I. Description of Epilepsy*

Epilepsy is a neurological disorder affecting an estimated 1.8 million Americans with estimated direct and indirect costs of illness to be approximately \$3 billion dollars. Epilepsy is characterized by the behavioral consequences of recurrent, spontaneous, transient paroxysms of abnormal brain activity. An epileptic attack or seizure may result in impaired consciousness, involuntary movements, autonomic disturbances, psychic or sensory disturbances. The fundamental etiology of epilepsy is thought to occur within the cerebral cortex or limbic cortex (hippocampus). Chronic epilepsy is the syndrome in which recurrent neuronal paroxysms that underlie ictal events are transient expression of more permanently physiological disordered cortex. In ascertaining the location and the diagnosis of epilepsy, one can determine patterns of uncoordinated cortex by examination of ictal and interictal EEG recordings. Interictal recordings of epilepsy patients have an appearance of brief discharges that can be recorded from the scalp. There is a noticeable spike-wave complex that is evident and is characterized by sharp negative transients followed by a slower wave. The EEG spike-wave complex reflects a summation of highly synchronized abnormal neuronal membrane potentials that upon inspection appear as large paroxysmal depolarization shifts followed by prolonged after depolarizations.

Epilepsy can be divided into the following categories based upon etiology: 1) primary epilepsy which is an intrinsic, nonprogressive, hereditary group of cerebral disturbances, 2) secondary epilepsy which is symptomatic of some known pathologic processes affecting the brain, and 3) reactive seizures which are characterized by natural reaction to physiologic stress or transient ischemic injury.

Epilepsy can be categorized into the following categories: partial seizures, generalized seizures, and seizures of unknown origin. Partial seizures are initiated (uni- or bilaterally) in discrete focal areas in the cortex and remain focal lesions. Generalized seizures begin either uni- or bilaterally and spread throughout the cortical tissue. In either case the mechanism of epileptogenic activity is to date unknown. However, there is evidence suggesting the etiology of epilepsy.

Partial seizures can be further subcategorized into: 1) simple partial seizure disorders, consciousness not impaired (with motor signs or symptoms, with somatosensory or special sensory symptoms (e.g. simple hallucinations, such as tingling, light flashes, buzzing), with autonomic signs and symptoms (e.g. epigastric sensation, pallor, sweating, flushing, piloerection and pupillary dilation), with psychic symptoms (e.g. disturbances of higher cerebral function (déjà vu, fear, distortion of time perception)); or 2) complex partial seizure disorders (simple partial onset following impairment of consciousness, impairment of consciousness at onset); or 3) partial seizures evolving to generalized tonic clonic seizures (simple partial seizures evolving to generalized seizures, complex partial seizures evolving to generalized seizures, and simple partial seizures evolving to complex partial seizures and further evolving to generalized seizures). A key feature of partial epilepsy is auras. These somatosensory or special sensory symptoms manifest as sensations described above and precede the seizure. There are cases whereby pharmacotherapy reduces the frequency and severity of partial seizures but may have little to no effect on aura sensation in partial epilepsy patients.

Generalized seizures are divided into 1) nonconvulsive seizures (absence seizures, atypical seizures, myoclonic seizures, or atonic seizures), or 2) convulsive seizures (tonic-clonic seizures, tonic seizures, or clonic seizures). Other seizure disorders that do not fit into the above categories are some cases of neonatal and infantile seizures.

There are other factors that one must consider when diagnosing seizure disorders. A generalized seizure may be the result sleep deprivation, alcohol or sedative drug withdrawal, use of convulsant drugs, fever, or acute head trauma. Furthermore, reversible toxic, infectious, or metabolic processes may induce recurrent generalized convulsions. Infantile febrile convulsions are an example of infancy and early childhood seizures that may or may not be indicative of a future epilepsy diagnosis.

Acquired epilepsy may be the result of congenital lesions, head trauma, infectious processes, brain tumors, cerebrovascular disease, systemic toxic and metabolic disturbances, hippocampal sclerosis, and miscellaneous disorders (collagen vascular disease, blood dyscrasias, cerebral gray matter degenerating diseases (allergic encephalopathy), presenile or senile dementias).

Epilepsy may be confused with clinical signs and symptoms of syncope, migraine, or pseudoseizures (nonepileptic psychogenic seizures). Usually, video/EEG monitoring of the patient during ictal and interictal periods allows trained personnel to distinguish epilepsy from these other clinical presentations.

## II. *Current Medical Management of Epilepsy*

For the majority of patients, epileptic seizures can be controlled with antiepileptic drug therapy (in many cases, monotherapy) and may be withdrawn if the patient is seizure free for an extended period, usually 2 years. Some patients do not become free of seizures, despite therapy compliance. Persistent epilepsy, aside from deleterious effects on health, has psychosocial, behavioral, and cognitive consequences, which often impose financial burdens to patients, their loved ones, and society.

Based upon accurate diagnosis of the seizure type and seizure-associated physiology, appropriate therapy to reduce seizure frequency, severity, and epilepsy-associated behaviors can be identified. Diagnosis of epilepsy involves both identification of the epileptic syndrome and the type of seizure. Syndromes are identified based upon age of onset, EEG recording analysis, location of the epileptic region or site of epileptogenesis, type of seizure. The drugs available for medical management of epilepsy are divided by their use in the clinic; common forms of epilepsy are treated differently than partial or secondarily generalized tonic-clonic seizures disorders.

The current pharmacotherapy has three main mechanisms of action: 1) reduction of sustained repetitive firing of a neuron by promoting the inactivation state of voltage-activated Na<sup>+</sup> channels; 2) enhanced GABAergic mediated presynaptic or postsynaptic inhibition of neural transmission; or 3) limiting the activation of specific voltage-activated Ca<sup>++</sup> channels (T current). Following these general mechanism of action, current anticonvulsant drugs act by 1) prolonging the inactivation of the Na<sup>+</sup> channels thereby reducing the ability of neurons to fire at high frequencies, 2) affecting GABAergic neurotransmission by reducing the metabolism of GABA, acting at the GABA receptor, enhancing the Cl<sup>-</sup> influx in response to GABA postsynaptically, or promoting presynaptic GABA release, or 3) reducing the flow Ca<sup>++</sup> T-type calcium channels reducing the pacemaker current that underlies the thalamic rhythm in spikes and waves in generalized absence seizures.

There are generally accepted first- and second-line drugs for each of the types of epilepsies and associated syndromes. For partial seizures they are carbamazepine and phenytoin (first-line) and gabapentin, lamotrigine, phenobarbital, primidone, tagabine, topiramate and valproic acid (second-line). For generalized seizures they are: absence seizures ethosuximide and valproic acid (first-line); lamotrigine (second-line); myoclonic seizures, valproic acid (first-line), acetazolamide, clonazepam, lamotrigine, or primidone (second-line)); tonic-clonic seizures valproic acid, carbamazepine, phenytoin (first-line), lamotrigine,

phenobarbital, primidone (second-line); absence epilepsy with onset in childhood  
ethosuximide (first-line), valproic acid, lamotrigine (second-line); absence seizures  
with onset in adolescence valproic acid (first-line), ethosuximide, lamotrigine  
(second-line)); juvenile myoclonic epilepsy valproic acid (first-line), acetazolamide,  
5 clonazepam, primidone, lamotrigine (second-line); infantile spasms (West's  
syndrome corticotropin (first-line), clonazepam, valproic acid)); Lennox-Gastaut  
syndrome valproic acid, lamotrigine (first-line), carbamazepine (second-line).

Because there is greater risk for refractory epilepsy in partial epilepsy  
patients, there has been greater demand for the development of novel treatment  
10 alternatives. Since 1993 and as stated above, the introduction of lamotrigine,  
topiramate, tiagabine, and gabapentin have changed the medical management of  
partial epilepsy. Although carbamazepine and phenytoin remain the mainstay  
therapies, these additions to the antiepileptic arsenal have provided therapeutic  
alternatives to this subset population of epilepsy patients.

15 In addition to AEDs, refractory epilepsy may benefit from surgical therapy to  
remove the site of epileptogenesis or implantation of a device to stimulate the vagus  
nerve. Surgical removal of cortical tissue can be successful therapy in up to two  
thirds of certain selected epilepsy and can reduce the seizure frequency and severity  
in others. However, surgical therapy of refractory epilepsy is underused, and is  
20 often a delayed procedure. It has been estimated that there are approximately 50,000  
epilepsy patients that could benefit from resective surgery, however, there are only  
an estimated 1,500 surgeries performed each year. Potential reasons for the  
profound difference in the potential number of surgical candidates and the number  
of procedures include: limited number of surgical teams performing the resective  
25 surgery; failure of primary physicians to identify potential candidates and to refer  
them to surgical centers; reluctance of third party payers to provide coverage for the  
costly presurgical diagnostic testing and procedures; and further, a reluctance on the  
part of the patient to voluntarily elect removal of cortical tissue.

Vagal nerve stimulation for the treatment of some patients with epilepsy has  
30 proven to be safe and well tolerated. A device is implanted in the upper quadrant  
that can be programmed to directly stimulate the vagal nerve. Stimulation of this  
autonomic nerve has lead to a documented 25% reduction of seizure frequency in  
refractory patients. The device does not appear to have similar efficacy when  
implanted in a partial epilepsy patient population. The use of the surgically  
35 implanted device has recently only been approved in the U.S. (June, 1997) for  
patients over 12 years of age with known refractory partial epilepsy. Transient  
hoarseness is a frequent side-effect of this device as a result of over-stimulation of  
the vagal nerve.

### III. *Limitations of Current Therapies for Epilepsy*

The limitations of current medical management of epilepsy are 1) partial response to therapy or refractory epilepsy, 2) undesired side effects, 3) continuing medical management of refractory or partial response in epilepsy patients, and 4) noncompliance.

#### Partial Response to Therapy and Refractory Epilepsy as a Therapeutic Limitation

Approximately 80% of patients with epilepsy are medically managed with current pharmacotherapy. In the remaining 20%, epileptic seizure frequency and severity are refractory to currently available medications. Medical personnel are left with attempting combination therapy of available anti-convulsive therapy. Standard regimens of multiple anticonvulsant therapy are fraught with greater tendency towards unwanted side effects. Interestingly, 20% of the primary generalized epilepsy patients and 35% of partial epilepsy patients are refractory. A poor response to anti-epileptic therapy may be result of many different therapeutic or diagnostic causes. Since the focus of therapeutic management of refractory epilepsy is combination antiepileptic drug therapy, the balance of beneficial therapy and the patient's intolerance of the adverse effects of the AEDs must be appropriately monitored.

#### Undesired Side Effects or Toxicities as a Therapeutic Limitation

All of the anti-epilepsy agents or compounds have undesired side effects. For example, nausea, dizziness, diplopia, ataxia, sedation, impaired mentation, hyperactivity, folic acid deficiency, leukopenia, elevated serum alkaline phosphatase levels, pruritis, blood dyscrasias, hirsutism, gingival hyperplasia, coarsening features, weight gain, and alopecia have been described for various anticonvulsant therapies.

Individuals with epilepsy have an increased rate of mortality as compared to the general population. Mortality is associated with treatment and with seizures and may include one or more of the following: trauma, burns, and drowning, habitual seizures with cardiopulmonary disease, severe aspiration, food bolus, and sudden unexplained death. Sudden unexplained death in epilepsy patients (SUDEP) has been reported as high as 1 in 270 patients that are refractory to antiepilepsy drugs, and is a statistic that does not include suicides.

Additional concern of combination therapy besides increased propensity to experience undesirable side effects is the effect of metabolic rates and blood levels of the combinations. There is ample literature on the effect one antiepileptic agent

has on another, for example carbamazepine decreases the blood levels of clanzepam, ethosuximide, methsuximide, primidone, tiagabine, topiramate, and valproic acid while increasing phenobarbital blood levels. Clonazepam decreases the blood levels of carbamazepine while decreasing primidone blood levels.

#### Continuous Medical Management as a Therapeutic Limitation

Antiepileptic drug (AED) therapy of epilepsy requires continuous medical monitoring. Factors involving lifestyle may trigger seizures in a patient diagnosed with epilepsy who have seemingly medically managed disease. For example, emotional stress, sleep deprivation, menstrual cycle, flickering lights and other sensory stimuli, alcohol use or withdrawal, or comorbidities (i.e. infections) may exacerbate seizures.

#### Noncompliance as a Limitation of Current Therapies

Noncompliance or partial compliance is a major concern in both monotherapy or combination therapy. Many patients who are in what appears to be remission, tend to noncompliance of their prescribed therapy. Determining plasma levels of the drug or drugs can monitor compliance, but this places an added burden on the patient and family members. Noncompliance can result from additional factors: missed medication, failure to refill the medication, a complicated dosing regimen, problems with memory or vision, postictal confusion, denial of medical condition, fear of teratogenic effects of the drug or drugs during pregnancy, concerns about the effects (both short and long-term) of the medication, and inability to afford the medication.

Clearly, for some patients, refined therapeutic management of seizure frequency and severity would have benefits above and beyond the clinical setting. Without many therapeutic alternatives to refine combination antiepileptic agent regimens, epilepsy poses a continued impact on health-related quality of life for each patient.

#### *IV. Impact of Pharmacogenomics on Drug Development for Epilepsy*

Genetic mechanisms of epilepsy have recently been described. However, the clinical genetics of seizure disorders has been a relatively slowly progressing field. Molecular genetic approaches have been useful to identify genes or gene clusters involved in linkage analysis.

Genetic polymorphism analysis and effects of antiepileptic drug therapy was recently described for the cytochrome P450 2C9 and 2C19 genes and these variance differences on the metabolic rates of phenytoin. The polymorphisms considered in

this study were the arg144cys and the ile359leu of the CYP2C9 gene and the \*1, \*2, and \*3 polymorphisms of CYP2C19. In this study of 134 Japanese patients, the mean maximal metabolic rates of phenytoin were 42% lower in individuals having the ile359leu genotype. From this analysis, the authors conclude that patients with the ile359leu genotype may not tolerate higher daily doses of phenytoin and may require genetic identification prior to implementation of medical strategies.

The evidence that a variance in a gene involved in a pathway that affects antiepilepsy drug response, indicates and supports the expectation that there is a likelihood that other genes have similar qualities to various degrees. As drug research and development proceeds to identify more lead candidate therapeutic interventions for epilepsy, there is possible utility in stratifying patients based upon their genotype for these yet to be correlated variances. Further, as described in the Detailed Description, methods for the identification of candidate genes and gene pathways, stratification, clinical trial design, and implementation of genotyping for appropriate medical management of a given disease is easily translated for epilepsy. As described below in section V. below there are likely gene pathways as are those that are outlined in the gene pathway Table 2 and in the gene pathway and indication matrix Table 7.

Optimization of GABAergic or ion channel modulation mediated therapy of epilepsy further demonstrates the utility of selection of a potential epilepsy patient that has a predisposing genotype in which selective AED or agents are more effective and or are safer. In considering an optimization protocol, one could potentially predetermine variance or variances within the GABAergic receptor, ion channel or ion channel mediated mechanisms of neurotransmission, or GABAergic receptor mediated intracellular mechanism of action that is preeminently responsible for drug response. By embarking on the previously described gene pathway approach, it is technically feasible to determine the relevant genes within such a targeted drug development program for epilepsy.

A sample of therapies approved or in development for preventing or treating the progression of symptoms of epilepsy currently known in the art is shown in table 29. In this table, the candidate therapeutics were sorted and listed by mechanism of action. Further, the product name, the pharmacologic mechanism of action, chemical name (if specified), and the indication is listed as well.

#### *V. Mechanism of Action Hypotheses for Novel Therapies for Epilepsy: Utility of Genotyping*

Further studies have demonstrated that there is a genetic component to epilepsy. These genetic factors may predispose by an individual to epilepsy by

inheriting one or more of the following 1) low threshold for aberrant seizure activity; 2) traits that underlie certain specific primary epilepsy disorders; and 3) a disease of the CNS in which there are associated structural disturbances that produce seizures. As described above there is an urgent need for the discovery and development of therapeutic alternatives for the medical management of epilepsy. Recent research and development programs have included the following exemplary hypothesis testing programs. In a first hypothesis, glutamate neurotransmitter pathway has been implicated in aberrant excitatory neurotransmission. Glutamate and aspartate are ligands for the N-methyl-D-aspartate receptors and ionophore receptors (AMPA and Glu 1-4). Research efforts have been dedicated to eliciting glutaminergic specific antagonists that may be productive inhibitors of aberrant excitatory neural signals or may be effective to attenuate neural modulatory mechanisms that are defective in epileptogenic tissue.

Another hypothesis includes the glycinergic pathway. Because glycine is an additional excitatory neurotransmitter, efforts to identify glycinergic specific ligands that may be of therapeutic benefit to prevent, reduce, or ablate seizure activity in cortical tissue. A third hypothesis is the histamine receptor ligands and tachykinin receptor ligands may be useful for neuromodulation of excitatory neurotransmission.

Further, there may be genes within pathways that are either involved in metabolism of neurotransmitters or are involved in metabolism of various drugs or compounds. In Tables 1-6, 12-17 and 18-23, there are listings of candidate genes and specific single nucleotide polymorphisms that may be critical for the identification and stratification of a patient population diagnosed with epilepsy based upon genotype. Current pathways that may have involvement in the therapeutic benefit of epilepsy include glutaminergic, serotonergic, dopaminergic, adrenergic, cholinergic, purinergic, GABAergic, glycinergic, taurine, oxytocin, vasopressin, calcium, potassium, or sodium channels, mitochondrial maintenance, protein maturation and degradation, and second messenger cascade gene pathways that are listed in Tables 1-6, 12-17, 18-23. One skilled in the art would be able to identify these pathway specific gene or genes that may be involved in the manifestation of epilepsy, are likely candidate targets for novel therapeutic approaches, or are involved in mediating patient population differences in drug response to therapies for epilepsy.

Based upon these varying hypotheses there are many products in development for epilepsy. Table 29 below lists current therapies that have not yet received U.S. marketing approval. The listed candidate therapeutic interventions



response in patients with epilepsy may be affected by polymorphisms in genes as described above.

#### **Example 14**

##### **Migraine**

###### *I. Description of Migraine*

Migraine is a neurological syndrome that has multiple, complex manifestations. Migraine with auras, unilateral throbbing, and associated nausea is the basic clinical symptomatic presentation. The premonitory phase may be up to 24 hours and may be associated with auras or alterations of mood, appetite, visual, sensory, or motor functions. Migraine headache is a unilateral throbbing that is associated with photophobia, hypacusis, polyuria, and diarrhea.

There are many clinical subtypes of migraine. Broadly, these subtypes can be distinguished by the presence or absence of auras. Migraines without auras are defined as the classic type. Migraines with auras can be further classified as 1) migraine with typical auras, 2) migraine with prolonged auras, 3) familial hemiplegic migraine, 4) basilar migraine, 5) migraine without headache, and 6) migraine with acute-onset aura. Additional migraine types include ophthalmologic migraine and retinal migraine.

###### *II. Current therapies for Migraine*

Migraine medical therapy depends on the acute or prophylactic nature of the therapy and whether the migraine is diagnosed as mild, moderate, or severe. Many patients will take a step approach to each separate migraine attack, starting with weakly acting agents and progressing to more potent drugs. For patients with severe migraine, therapy includes prophylactic management.

###### **Therapy for Acute Migraine**

Mild migraine is a headache that may be accompanied by nausea, is unilaterally throbbing, and can be treated by nonprescription analgesics. Patients infrequently consult a neurologist for care of mild migraines because the level of impairment imparted by the headache portion is not debilitating and is relatively short lived. Mild migraine is thus treated with aspirin, acetaminophen, ibuprofen, indomethacin, naproxen sulfate, and in some cases antiemetic drugs (diphenhydramine, prochlorperazine, promethazine, and metchlorpramide).

Moderate migraine is generally characterized by similar symptoms of mild migraine, however the frequency and or severity are increased. Patients with

moderate migraine are generally not relieved with non-narcotic analgesics, and require medications that combine aspirin or acetaminophen with a mild sedative or  $\alpha$  and  $\beta$  adrenergic receptor mediated vasoconstriction.

Severe migraine is characterized by similar symptoms as mild and moderate migraine. However, the severity and frequency of headache is debilitating. Patients seek relief from the headache pain in the acute stage and frequently require prophylactic maintenance therapy. The drugs used for the therapy of acute migraine are members of the ergot alkaloid family or sumatriptan.

The ergot alkaloids are partial agonists and antagonists for a variety of receptor types; serotonergic, adrenergic, dopaminergic, muscarinic, and GABAergic. Synthetic products with similar chemical structures to ergotamine predominantly are agonists at the serotonin subtype 1D or 1B. Both of these two subtypes act by inhibiting adenylyl cyclase activity in cortical neurons. Ergotamine is also a vasoconstrictor; this activity is thought to occur through activation of the  $\alpha$ 1 adrenergic receptor system. Ergotamine is metabolized by undefined pathways and metabolites are excreted primarily in the bile. The bioavailability of ergotamine is approximately 1% due the potent first pass effect after parenteral delivery of the drug and erratic absorption between individuals.

Sumatriptan is another drug used for the acute, severe migraine attacks. Sumatriptan is a serotonin 1B, 1D selective receptor agonist. Because these receptor subtypes are auto receptors, activation of 5HT1B and 5HT1D receptors can act by controlling the release of the serotonin and other neurotransmitter release. Sumatriptan may also be efficacious in the treatment of migraine because it may block proinflammatory receptors at the level of nerve terminal in the perivascular space.

Other drugs used as adjunct therapy for acute, severe migraine attacks are corticosteroids and opioid analgesics. Due to their addictive qualities, opioid or narcotic analgesics are limited to acute, infrequent attacks.

### Prophylactic Therapy of Migraine

There are currently six classes of standard treatments for the prophylactic therapy of migraine. They are 1) tricyclic antidepressants (amitriptyline), 2) 5HT antagonists (methysergide), 3)  $\beta$  adrenergic receptor antagonists (propranolol, timolol, atenolol, metoprolol, nadolol), 4) monoamine oxidase inhibitors (depranil), 5) calcium channel blockers (verapamil, flunarizine), and 6) anticonvulsants (divalproex sodium, chlorpromazine). The criteria for the selection of prophylactic therapy are 1) patient has 6 or more headaches each month, 2) symptomatic medications are contraindicated or ineffective, 3) medication is necessary more than

twice each week, and 4) there is an expressed need on the part of the patient to prevent infrequent attacks, e.g. hemiplegic migraine, those headaches producing profound disruption, or those associated with a risk of stroke. The ultimate choice of the prophylactic medication is based upon the measured effect on the type of migraine and the patient's willingness to withstand the associated side effects.

### *III. Limitations of Current Therapies for Migraine*

The current therapy of migraine includes management of acute attacks of the mild, moderate and severe categories. Therapies of severe migraine further include prophylactic therapies. Regardless of the acute or prophylactic nature of the therapy, there are both efficacy and toxicity limitations in which migraine remains problematic for medical management.

#### Toxicity or Undesired side effects of Acute Migraine Therapy

Ergotamine and its derivatives are useful drugs for the management of acute severe migraine attacks, however there are side effects associated with administration of the drug. Ergotamine is an activator of the CNS emetic centers, and nausea and vomiting are a frequent side effect that can be confused with a manifestation of the migraine attack. Other undesirable side effects are weakness of the legs, muscle pains, numbness and tingling of toes, and transient tachy- or bradycardia.

A known side effect of sumatriptan is coronary vasospasm and it is thus contraindicated in patients with ischemic heart disease or Prinzmetal's angina.

#### Limitations of Prophylactic Migraine Therapy

Although prophylactic therapy for migraine can reduce the frequency and intensity of the migraine attack, there are patients that achieve dramatic improvement and there are those that achieve only a 50% reduction, indicating a limited efficacy and benefit for a significant population subgroup. In those patients, the severity and intensity must be significant to require daily prophylactic medication.

Of the six categories of prophylactic agents all have associated side effects that may or may not be tolerable to each individual patient. They are 1) tricyclic antidepressants: sedation, dry mouth, weight gain, tremor, cardiac arrhythmias, aggravation of angle-closure glaucoma, and difficulty in urinating; 2) 5HT antagonist: weight gain, muscle cramps, vasoconstriction, and retroperitoneal pleuroperitoneal and subendocardial fibrosis; 3)  $\beta$  adrenergic receptor antagonists: aggravation of asthma, bradycardia, hypotension, fatigue, depression, masking the

symptoms of diabetes mellitus; 4) monoamine oxidase inhibitors: orthostatic hypotension, insomnia, and nausea; 5) calcium channel blockers: are not frequently used, however are associated with constipation and orthostatic hypotension; and 6) anticonvulsants: nausea, fatigue, weight gain, alopecia, tremor, liver dysfunction, and neural tube defects in developing embryos.

The least desired effect of prolonged prophylactic therapy of migraine is the associated increased frequency of headaches. Headaches, not of the migraine type, can occur daily and are related to rebound withdrawal from frequent use of the acute antimigraine medication. Patients experiencing this type of headache pattern are said to have transformed migraine and often experience episodic migraine attacks superimposed on their daily headaches. Ergotamines are frequently associated with chronic daily headaches, as are the triptans. Unfortunately, patients experiencing daily headaches are less likely to respond to acute therapy or any other preventative medications. Withdrawal of other migraine medications further render the patient more susceptible to daily headaches. Therefore, it is beneficial to prevent transformed migraine and chronic daily headaches. Drugs known to be associated with transformed migraine are generally limited to occasional use in patients that have greater than two migraines each month. It is additionally recommended for patients that experience more frequent headaches requiring over-the-counter or prescription medications be put on a rotating schedule.

#### *IV. Impact of Pharmacogenomics on Drug Development for Migraine*

As described above, there is evidence to suggest that there are efficacy and safety different responses to drug therapy within the migraine patient population. Although not all of these responses may be attributable to genotypic differences, it is expected that if stratification based upon genotype were performed, a reasonable correlation between drug response and genotype may become obvious. As described below, there are gene pathways that are involved with current drug therapy and those that may be potentially involved in the future. As described in the Detailed Description, methods for the identification of candidate genes and gene pathways, stratification, clinical trial design, and implementation of genotyping for appropriate medical management of a given disease is easily translated for migraine and patients diagnosed with migraine. As described below in section V. below there are likely gene pathways as are those that are outlined in the gene pathway Table 2 and matrix Table 7.

Optimization of serotonergic, nonsteroidal antiinflammatory, or cerebral vasoconstrictor mediated mechanism of therapy of migraine further demonstrates the

utility of selection of a potential migraine patient that has a predisposing genotype in which selective anitmigraine or agents may be more effective and or have an more desirable safety profile. In considering an optimization protocol, one could potentially predetermine variance or variances within the serotonergic receptor pathway, nonsteroidal aninflammatory pathway, or serotonergic receptor or nonsteroidal antiinflammatory mediated intracellular mechanism of action that is preeminently responsible for antimigraine drug response. By embarking on the previously described gene pathway approach, it is technically feasible to determine the relevant genes within such a targeted drug development program for migraine.

A sample of therapies approved or in development for preventing or treating the progression of migraine currently known in the art is shown in Table 31. In this table, the candidate therapeutics were sorted and listed by mechanism of action. Further, the product name, the pharmacologic mechanism of action, chemical name (if specified), and the indication is listed as well.

Pharmacogenomics studies for these drugs, as well as other agents, drugs, compounds or candidate therapeutic interventions, could be performed by identifying genes that are involved in the function of a drug including, but not limited to is absorption, distribution metabolism, or elimination , the interaction of the drug with its target as well as potential alternative targets, the response of the cell to the binding of a drug to a target, the metabolism (including synthesis, biodistribution or elimination) of natural compounds which may alter the activity of the drug by complementary, competitive or allosteric mechanisms that potentiate or limit the effect of the drug, and genes involved in the etiology of the disease that alter its response to a particular class of therapeutic agents. It will be recognized to those skilled in the art that this broadly includes proteins involved in pharmacokinetics as well as genes involved in pharmacodynamics. This also includes genes that encode proteins homologous to the proteins believed to carry out the above functions, which are also worth evaluation as they may carry out similar functions. Together the foregoing proteins constitute the candidate genes for affecting response of a patient to the therapeutic intervention. Using the methods described above, variances in these genes can be identified, and research and clinical studies can be performed to establish an association between a drug response or toxicity and specific variances.

#### *V. Description of Mechanism of Action Hypotheses for Future Migraine Drug Development*

The pathogenesis of migraine includes the following theories: vascular, depression of cortical electrical activity, serotonergic abnormalities, alteration of

neurotransmitter modulation, and modulation of neuroendocrine mechanisms. These are described briefly below.

The vascular theory of migraine posits that there is abnormal cerebral blood flow and it apparently plays a pivotal role in the clinical symptoms of migraine. Studies have shown that a decrease in cerebral blood flow during an aura and an increase in blood flow during headache occur in migraine patients. This theory is somewhat substantiated indirectly by the pharmacologic action of therapies for acute migraine and prophylaxis, as previously described.

There have been additional studies that point to a mechanism of spreading depression of cortical electrical activity and a concurrent alteration of blood flow. This theory suggests that focal reduction of electrical activity and concurrent increase in blood flow occurs focally and spreads across the hemisphere at a rate of 2-3 mm each minute. This spreading hypothesis has been refined to a description of migraine as an evolving process in the cerebral cortex that occurs secondarily to decreased cortical function, decreased cortical metabolism, and or vasoconstriction of cortical arterioles.

Many studies have addressed the effect of serotonergic mechanism of the pathogenesis of migraine. These studies used the following premises: 1) there have been reports of decreased concentrations of serotonin in platelets and plasma, 2) increased levels of serotonin and serotonergic metabolites in urine, 3) lastly, migraine may be precipitated by abnormal release of biogenic amines, a theory borne out of the fact that reserpine and fenfluramine can precipitate a migraine attack.

Other theories propose that alterations of neurotransmitter systems e.g. nitric oxide, glutamate, and opioid receptors may be part of the pathogenesis of migraine. Further, Some studies have included anatomical differences in the raphe system and within the cerebral vasculature as well as alterations of the autonomic nervous system.

Therapy of migraine is dependent on the appropriate diagnosis, as well as the type, frequency, and severity of the throbbing headache. Upon diagnosis, patient education to identify and avoid trigger factors is a critical first step in all patients.

Trigger factors may include but are not exclusive to alcohol (red wine), foods (chocolate, certain cheeses), irregular sleep patterns, and acute changes in stress levels. Triggers may also come from environmental factors, such as time-zone shifts, high altitudes, or barometric changes. In women, menstrual cycles may trigger a migraine attack. These trigger factors suggest that there are complicating factors to include in any pathophysiologic hypothesis of migraine, and that these hypotheses may include neuroendocrine, endocrine, and other metabolic factors.

Further, there may be genes within pathways that are either involved in metabolism of neurotransmitters or are involved in metabolism of various drugs or compounds. In Tables -6, 12-17 and 18-23, there are listings of candidate genes and specific single nucleotide polymorphisms that may be critical for the identification and stratification of a patient population diagnosed with epilepsy based upon genotype. Current pathways that may have involvement in the therapeutic benefit of migraine include glutaminergic, serotonergic, dopaminergic, adrenergic, cholinergic, GABAergic, nitric oxide, peptide hormone processing, opiates, tachykinin, bradykinin, corticotropin releasing hormone, calcitonin/calcitonin gene related peptide, calcium channel, hemostasis, and second messenger cascade gene pathways that are listed in Tables -6, 12-17 and 18-23. One skilled in the art would be able to identify these pathway specific gene or genes that may be involved in the manifestation of migraine, are likely candidate targets for novel therapeutic approaches, or are involved in mediating patient population differences in drug response to therapies for migraine.

Based upon these varying hypotheses as stated above, there are many products in development for migraine. Table 31 below lists current therapies that have not yet received U.S. marketing approval.

### **Example 15**

#### **Psychosis**

Psychosis is a general term for major mental disorder characterized by loss of contact with reality, often manifested by disordered thought, delusions or hallucinations. Psychosis can be part of several distinct psychiatric diseases, including schizophrenia, manic-depressive disease, severe depression with psychotic features, organic psychotic disorders, as well as in alcohol or drug intoxication and acute idiopathic psychotic illnesses. The most common of these is schizophrenia. The antipsychotic drugs are also used to treat non-psychiatric conditions such as, for example, nausea and vomiting, movement disorders associated with neurodegenerative diseases such as Huntington's disease and Tourette's syndrome, pruritis and chronic hiccough. Example 11 focuses predominantly on schizophrenia, however similar analysis, in terms of the relevant pathways, genes, polymorphisms and analytical methods for establishing relationships between polymorphisms and drug responses, would obtain in all the other diseases treated with antipsychotic drugs. Criteria for the diagnosis of schizophrenia and other psychoses, as well as diagnostic criteria for the other disorders treated with antipsychotics, are well established. (Diagnostic and

Statistical Manual of Mental Disorders, 4th ed., American Psychiatric Association Press, Washington, D.C., 1994.)

## II. Current Medical Management of Schizophrenia

5 Over 15 drugs are approved for treatment of psychosis in the US. They include the so-called conventional or typical antipsychotic drugs and the more recently introduced atypical antipsychotic drugs. The former class includes phenothiazines (e.g. chlorpromazine, the first antipsychotic to be widely used), thioxanthenes (e.g. thiothixene), butyrophenones (e.g. haloperidol, one of the most  
10 useful conventional antipsychotics) and other heterocyclic compounds. The atypical antipsychotics include compounds such as clozaril (the first, and best studied member of the class), risperidone, olanzapine, quetiapine, ziprasidone and iloperidone. Some drugs, such as loxapine, have pharmacology intermediate between that of the typical and atypical drugs.

15 The typical antipsychotics are believed to act predominantly by antagonizing dopamine receptors, particularly D2-dopamine receptors. These medications can be effective in reducing the positive symptoms of schizophrenia (hallucinations, delusions) but are generally not effective at alleviating the negative symptoms (withdrawal, flat affect, anhedonia, lack of will), nor do they generally result in  
20 improved cognitive function. In fact, negative symptoms and cognitive function may worsen on typical antipsychotics. Typical antipsychotics exhibit dose dependent efficacy, and the optimal dose for a given patient must be determined empirically by gradually increasing the dose until adequate control of symptoms is achieved (without unacceptable side effects – see below). A therapeutic dose is  
25 usually reached within 2-3 weeks of initiating therapy.

The atypical antipsychotic drugs have replaced the typical agents as front line therapy for schizophrenia and other psychoses because they have a beneficial impact on the negative symptoms as well as the positive symptoms of schizophrenia, and because, based on recent research, they may also improve cognitive function.  
30 The atypical drugs affect a number of neurotransmitter systems, with modulation of serotonergic neurotransmission – particularly 5HT<sub>2C</sub> receptor antagonism, a prominent effect in addition to modulation of dopaminergic function.. The best studied of this class of drugs is clozapine, which binds dopamine receptors with low affinity, and also interacts with muscarinic, adrenergic, serotonergic, and  
35 histaminergic receptors. The table below depicts the relative receptor affinity (0-5



on a scale of 5, where 5 indicates a high affinity interaction) of a conventional drug (haloperidol) and an atypical drug (clozapine).

#### Relative Receptor Affinities of Haloperidol and Clozapine

|             | Neurotransmitter Receptor Subtype |    |                   |                   |            |            |    |    |
|-------------|-----------------------------------|----|-------------------|-------------------|------------|------------|----|----|
|             | D1                                | D2 | 5HT <sub>2A</sub> | 5HT <sub>1A</sub> | $\alpha$ 1 | $\alpha$ 2 | H1 | M1 |
| Haloperidol | +3                                | +4 | +1                | 0                 | +2         | 0          | 0  | 0  |
| Clozapine   | +2                                | +2 | +1                | +3                | +3         | +3         | +4 | +5 |

The effectiveness of the atypical antipsychotic drugs has revealed the inadequacy of a simplistic dopamine excess hypothesis of schizophrenia. The clinical effects of the atypical antipsychotic drugs are likely to reflect the summation of a complex set of interactions with a variety of neurotransmitter receptors. Interpatient differences in the function, levels or anatomical distribution of these different receptors are likely to account for a substantial fraction of interpatient variation in response to atypical antipsychotic drugs. Further, the function, levels and anatomical distribution of receptors is largely under genetic control, as is the associated biosynthetic, catabolic, recycling and signal transduction machinery. An understanding of the specific genetic variants that have major effects on drug efficacy would allow a far more sophisticated selection of appropriate therapy and dose than is possible currently.

#### *III. Limitations of Current Therapies*

The chief limitations of antipsychotic medicines are (i) conventional and atypical neuroleptic agents do not reduce the signs and symptoms of schizophrenia in all patients (an estimated one third to one quarter of psychotic patients are resistant to therapy); (ii) a wide range of serious adverse effects. Further, it is impossible to predict the response of any given patient, particularly the mix of drug effects on positive symptoms, negative symptoms, cognitive deficits and side effects. As a result, selection of therapy is at present completely empirical. This approach is costly, as (i) multiple physician visits may be required before an optimal dose of an effective agent is attained; (ii) even after determining an effective drug regiment, the long term effects of therapy in specific patients generally remain unknown, particularly with respect to side effects; (iii) these problems result in low rates of compliance with therapy. Hence there is a need for tools that would allow the prospective identification of patients likely to be responsive to - and free from short or long term side effects from - a particular drug.

### Efficacy Limitations

The dilemma confronting psychiatrists and other clinicians selecting therapy for psychotic patients has been described by Baldessarini in Goodman and Gilman's The Pharmacological Basis of Therapeutics (9th edition) as follows: "No one drug or combination of drugs has a selective effect on a particular symptom complex in groups of psychotic patients; although individual patients may appear to do better with one agent than another, this can be determined only by trial and error". Thus, a clinician selecting therapy for a newly diagnosed psychotic patient, generally selects a compound with which he is comfortable, based on past experience. If that agent is not effective, or is producing a side effect, then a second agent is selected, again, entirely based on the physicians clinical judgement, and so on. This approach to optimization of pharmacotherapy has both medical and economic drawbacks. From the medical point of view, it does not always result in the selection of optimal treatment, with the attendant drawbacks in patient compliance. From an economic viewpoint the number of physician visits required to reach an effective dose of an effective drug are greater than necessary, and some patients may require hospitalization during the period when various drug regimens are being tested. There are other costs of using less than optimal therapy: (i) a patient might experience an improvement in cognitive symptoms on an optimal drug that would allow performance of a regular job; suboptimal therapy, even while adequately controlling positive symptoms, might not be sufficient to enable job performance. (ii) An optimal drug would minimize side effects, and thereby reduce physician visits, while also resulting in greater compliance. (Noncompliance is likely to ultimately lead to more hospitalization.) Determination of an optimal dose of an antipsychotic is another challenging aspect of therapy with these agents. Baldessarini (Goodman and Gilman, 9th ed.) writes: "Optimal dosage of antipsychotic drugs requires individualization to determine doses that are effective, well-tolerated, and accepted by a patient. Careful observation of the patients changing response is the best guide to dosage." As with selection of an optimal agent, discussed above, the determination of an optimal dose presently requires multiple physician visits. Clearly some fraction of interpatient variation in optimal dose level is likely due to genetic, and consequent biochemical differences between patients. Such differences may involve drug metabolizing enzymes or proteins that mediate pharmacodynamic effects. A list of such proteins is provided in Tables 1-6. Many typical antipsychotic drugs are metabolised by cytochrome P450 enzymes, with consequent wide interpatient variation in pharmacokinetic parameters. Further, many antipsychotic drugs are converted to active metabolites which can have

therapeutic effects or side effects. The metabolism of the tricyclic atypical drugs (clozapine, olanzapine, and quetiapine) occurs via N+-oxidation, N-glucuronidation, and phases 1 and 2 metabolism with final glucuronidation before renal excretion. The non-tricyclic atypical antipsychotic drugs (e.g. risperidone, sertindole and ziprasidone) have diverse chemical structures and there is less data on their metabolism, but it appears to include diverse phase 1 biotransformation reactions. As a rule, conventional antipsychotics are mainly effective against positive symptoms (hallucinations, delusions, illusions), while not significantly ameliorating negative symptoms (withdrawal and flat affect). They are also associated with a high incidence of adverse effects, particularly extrapyramidal symptoms (EPS) and tardive dyskinesia. Atypical antipsychotics constitute a significant improvement, in that they are at least as effective as conventional drugs against positive symptoms, they show at least some effectiveness against negative symptoms and, according to recent studies, they may also produce improvement in the cognitive deficits associated with schizophrenia (e.g. attention, executive function, short and long term memory), while causing substantially fewer extrapyramidal symptoms.

#### Toxicity Limitations

Unfortunately, conventional anti-psychotic drugs are uniformly associated with undesirable dose-dependent side effects. These include (but are not limited to) extrapyramidal effects, electrocardiogram abnormalities, sedation, weight gain, cognitive deficits, sexual or reproductive dysfunction, blood dyscrasias (particularly agranulocytosis associated with clozapine), , neuroleptic malignant syndrome (parkinsonism with catatonia), jaundice, skin reactions, epithelial keratopathy and seizures. Skin reactions include urticaria and dermatitis and are usually associated with phenothiazines. Epithelial keratopathy and corneal opacities are associated with chlorpromazine therapy. In extreme cases these effects impair vision, but they tend to spontaneously disappear upon discontinuation of chlorpromazine.

The extrapyramidal side effects of conventional neuroleptics include dystonia (facial grimacing, torticollis, oculogyric crisis), akathisia (feeling of distress or discomfort leading to restlessness or constant movement), and parkinsonian syndrome (rigidity and tremor at rest, flat facial expression).

Tardive dyskinesia is a common side effect of long term usage of conventional neuroleptic drugs. Tardive dyskinesia is a syndrome of abnormal involuntary repetitive, painless movements. These movements vary in intensity over time, dependent on the level of arousal or emotional distress. Typically there are

quick choreiform (ticlike) movements of the face, eyelids (blinks or spasms), mouth (grimaces), tongue, extremities, or trunk. Increasing the dose of the conventional neuroleptic agent can reverse extrapyramidal effects short term, but at the cost of more severe dyskinesia long term. Not infrequently a clinician is compelled to  
5 change medication for a patient with adequately controlled schizophrenia because of dose related tardive dyskinesia or other extrapyramidal side effects..

Another important side effect of many antipsychotic drugs is QT wave prolongation, which has recently resulted in the withdrawal of an atypical antipsychotic compound. Cardiac conduction abnormalities associated with  
10 antipsychotic therapy have resulted in patient deaths, presumably as a consequence of ventricular tachycardias. The mechanism of the conduction abnormalities appears to involve drug binding to cardiac potassium channels and consequent interference with repolarization current. Sertindole, for example, is a new antipsychotic agent that binds with high affinity (3-14 nM, depending on conditions) to and antagonizes  
15 HERG, a cardiac potassium channel. The degree of interpatient variation in these effects is not well characterized. Genes likely to account for these differences encode potassium channels (which may also have some role in the central actions of these compounds), sodium channels and the genes associated with inherited forms of long QT wave syndrome (QT1, QT2, QT3, QT4, QT5 and QT6).

20 Yet another important side effect of antipsychotic drugs is weight gain which can lead to obesity.

#### *IV. Impact of Genotyping on Drug Development for Schizophrenia*

Most traditional neuroleptics have a narrow therapeutic-to-toxic index, and thus, the novel antipsychotics are the result of a search to substantially widen the  
25 distance between the dose that treats psychosis and the one that produces adverse effects. In vitro binding profiles have been created for the atypical antipsychotics that have been approved by the U.S. Food and Drug Administration (FDA)-clozapine, olanzapine, and risperidone and those that are under FDA review-quetiapine and sertindole. These profiles, which were compared with that of the  
30 typical neuroleptic haloperidol, provide guidance for predicting the adverse effects produced by these drugs. Most conventional antipsychotics have central nervous system effects, particularly extrapyramidal symptoms (EPS) and tardive dyskinesia, sedation, and dulling of cognition. Other adverse effects of the typical antipsychotics include the neuroleptic malignant syndrome, orthostatic hypotension,  
35 changes in liver function, anticholinergic and antiadrenergic side effects, sexual

dysfunction, and weight gain. The newer agents have a lower incidence of EPS and tardive dyskinesia, while weight gain and changes in blood pressure and liver function tests are adverse effects that have been associated with the use of the newer agents. The favorable side effect profile of these new antipsychotics is likely to  
5 make patients more willing to continue treatment, and thus these agents represent a step forward in the treatment of patients with severe, chronic mental illness.

This paper reviews the current literature describing the metabolism of both multi-receptor clozapine analogue atypical antipsychotic drugs (clozapine, olanzapine, and quetiapine) and serotonin-dopamine antagonist atypical  
10 antipsychotic drugs (risperidone, sertindole and ziprasidone), to highlight the significance of those data in the context of clinical practice. The former group of atypical antipsychotic drugs shares a similar tricyclic structural nucleus and are metabolized through three major categorical metabolic pathways--N+-oxidation, N-glucuronidation, and phases 1 and 2 biotransformation with final glucuronidation  
15 before renal excretion.

There have been reports of polymorphisms in key genes that affect neuroleptic activity in schizophrenic patients. For example, within the dopamine D4 receptor subtype, there are known tandem repeats in exon 3. In a recent study, schizophrenic patients on maintenance doses of chlorpromazine were stratified into  
20 two groups, one having 2 tandem base pair repeats and the other having 4 tandem base pair repeats. Thirty-four percent of group one patients and 62% of group two patients had a favorable response to chlorpromazine therapy during acute stage treatments. The presence of homogeneous four 48 base pair repeats in both alleles in exon 3 of the dopamine D4 receptor subtype thus appears to be associated with  
25 beneficial chlorpromazine response.

Recently, a study of the serotonin receptor subtype 6, polymorphism (T267T vs. C267T) in a group of patients refractory to clozapine therapy was reported. In this study, it appeared that the T267T genotype patients were more likely to respond to continued therapy than those patients with C267T genotype patients.  
30 A recent report documented a correlation of the serotonin 5HTC2 receptor subtype biallelic polymorphism and neuroleptic efficacy. A significant number of schizophrenic patients homozygous for the allele C2 who responded unsatisfactorily to antipsychotic medication as compared to control.

Three polymorphisms in the serotonergic receptors, i.e. 5HT2A (T102C);  
35 5HT2C (cys23ser); and 5HT2A (his452tyr) have reports of positive or negative correlation with efficacy of antipsychotic therapies. This disparity in the literature

will, in the future, be further examined in schizophrenic patient populations and correlation may be discovered.

The evidence that a variance in a gene involved in a pathway that affects neuroleptic drug response, indicates and supports the theory that there is a likelihood that other genes have similar qualities to various degrees. As drug research and development proceeds to identify more lead candidate therapeutic interventions for schizophrenia, there is possible utility in stratifying patients based upon their genotype for these yet to be correlated variances. Further, as described in the Detailed Description, methods for the identification of candidate genes and gene pathways, stratification, clinical trial design, and implementation of genotyping for appropriate medical management of a given disease is easily translated for schizophrenia. As described below in section V. below there are likely gene pathways as are those that are outlined in the gene pathway Table 2 and matrix table 7.

Identification of pathophysiologic relevant variance or variances and potential therapies affecting those allelic genotypes or haplotypes will speed the drug development. There is a need for therapies that are targeted to the disease and symptom management with limited or no undesirable side effects. Identification of a specific variance or variances within genes involved in the pathophysiologic manifestation of schizophrenia and specific genetic polymorphisms of these critical genes may assist the development of novel neuroleptic agents and the identification of those patients that may best benefit from therapy of these candidate therapeutic alternatives.

By identifying allelic variances or haplotypes in genes that indirectly affects efficacy, safety or both one could target specific secondary drug or agent therapeutic actions that affect the overall therapeutic action of conventional, atypical, or novel neuroleptic action.

A sample of therapies approved or in development for preventing or treating the progression of symptoms of schizophrenia currently known in the art is shown in Table 35. In this table, the candidate therapeutics were sorted and listed by mechanism of action. Further, the product name, the pharmacologic mechanism of action, chemical name (if specified), and the indication is listed as well.

*V. Mechanism of Action Hypotheses for Novel Therapies for Schizophrenia: Utility of Genotyping*

The underlying etiology of schizophrenia is not established, however there is compelling evidence that modulation of several neurotransmitter systems has an impact on the disease. As discussed above, conventional anti-psychotic drugs, effective in the management of schizophrenia, are dopamine antagonists, specifically D2-receptor antagonists, which block dopaminergic neurotransmission in the forebrain. Additionally, drugs such as mescaline and amphetamines, which are known to stimulate dopaminergic pathways, have been shown to induce psychotic symptoms. Evidence of dysfunctional serotonergic neurotransmission in schizophrenia includes evidence of altered serotonin receptor density, altered serotonin metabolism, and the evidence that serotonin receptors appear to be important targets for the atypical neuroleptics.

Based on current knowledge, there are three hypotheses that underscore the utility of polymorphic genotype analysis within the schizophrenic population. In the first, it could be considered that endogenous dopamine levels and consequential dopaminergic tone varies among schizophrenic patients, affecting response to receptor antagonists. These genetic DNA variations may affect brain neurotransmitter modulation of dopaminergic transmission and dopaminergic receptor mediated intracellular mechanisms among schizophrenic patients. In the second hypothesis, genetic DNA variations may affect the level of expression and brain distribution of dopamine receptors, imparting a variation in drug response among schizophrenia patients. Further, consideration of other endogenous neurotransmitters, i.e. serotonin, levels and consequential endogenous neurotransmitter tone varies among schizophrenic patients, affecting response to neurotransmitter receptor ligands or neurotransmitter receptor mediated intracellular mechanisms.

Further, there may be genes within pathways that are either involved in metabolism of neurotransmitters or are involved in metabolism of various drugs or compounds. In Tables 1-6, 12-17, and 18-23, there are listings of candidate genes and specific single nucleotide polymorphisms that may be critical for the identification and stratification of a patient population diagnosed with epilepsy based upon genotype. Current pathways that may have involvement in the therapeutic benefit of schizophrenia include glutaminergic, serotonergic, dopaminergic, adrenergic, cholinergic, histaminergic, GABAergic, glycinergic, opiates, cholecystokinin, neurotensin, tachykinin, calcium channels, and second messenger cascade gene pathways that are listed in Tables 1-6, 12-17, and 18-23. One skilled in the art would be able to identify these pathway specific gene or genes that may be involved in the manifestation of schizophrenia, are likely candidate

targets for novel therapeutic approaches, or are involved in mediating patient population differences in drug response to therapies for schizophrenia.

### **Example 16**

#### **Effect of Pharmacokinetic parameters on Efficacy of Drugs and Candidate Therapeutic Interventions**

The efficacy of a compound is determined by a combination of pharmacodynamic and pharmacokinetic effects. Both types of effect are under genetic control. In the present invention, the genetic determinants of efficacy are discussed in terms of variation in the genes that encode proteins responsible for absorption, distribution, metabolism, and excretion of compounds, i.e. pharmacokinetic parameters.

The pharmacokinetic parameters with potential effects on efficacy include absorption, distribution, metabolism, and excretion. These parameters affect efficacy broadly by controlling the availability of a compound at the site(s) of action. Interpatient variability in the availability of a compound can result in undertreatment or overtreatment, or in adverse reactions due to levels of a compound or its metabolite(s). Differences in the genes responsible for pharmacokinetic variation, therefore, can be a potential source of interpatient variability in drug response.

#### ***Impact of Stratification Based Upon Genotype in Drug Development for Drugs, Compounds, or Candidate Therapeutic Interventions that may Efficacy***

Clozapine induced agranulocytosis has been associated in some reports with specific HLA haplotypes or with HSP70 variants. These reports suggest that a gene within the HLA region is associated with agranulocytosis in response to clozapine therapy. In a recent study, two ethnic groups were analyzed for genetic markers for agranulocytosis. Tumor necrosis factor microsatellites d3 and b4 were found in higher frequencies in patients that experience clozapine-induced agranulocytosis. These data, while they need to be confirmed by additional studies, are suggestive that tumor necrosis factor polymorphisms may also be associated with clozapine-induced agranulocytosis.

In this invention we provide additional genes and gene sequence variances that may account for variability in toxic responses. The Detailed Description above demonstrates how identification of a candidate gene or genes (e.g. gene pathways), genetic stratification, clinical trial design, and diagnostic genotyping can lead to improved medical management of a disease and/or approval of a drug, or broader use of an already approved drug. Gene pathways including, but not limited to, those that are outlined in the gene pathway, Tables 1-6, preferably Table 3, are useful in



identifying the sources of interpatient variation in efficacy as well as in the adverse events summarized in the column headings of Table 8. Discussed in detail below are exemplary candidate genes for the analysis of pharmacokinetic variability in clinical development, using the methods described above.

5 Advantages of Inclusion of Pharmacogenetic Stratification in Clinical Development of Agents: Impact on Efficacy

As an example of identification of the primary gene and relevant polymorphic variance that directly affects efficacy, safety, or both one could select an gene pathway as described in the Detailed Description, and determine the effect  
10 of genetic polymorphism and therapy efficacy, safety, or both within that given pathway. For example, referring to Table 8, genes involved in absorption and distribution, phase I and phase II metabolism, and excretion the optimization of therapy of by an agent known to have an efficacious effect by determining whether the patient has a predisposing genotype in which the selected agents are more  
15 effective and or are more safe. In considering an optimization protocol, one could potentially predetermine the genotypic profile of these genes involved in the manifestation of the adverse effect, or those genes preeminently responsible for drug response. By embarking on the previously described gene pathway approach, it is technical feasibility to determine the relevant genes within such a targeted drug  
20 development program.

Example 17

Drug-Induced Toxicity: Blood Dyscrasias

I. Description of Blood Dyscrasias

25 Blood dyscrasias are a feature of over half of all drug-related deaths and include, but are not limited to, bone marrow aplasia, granulocytopenia, aplastic anemia, leukopenia, lymphoid hyperplasia, hemolytic anemia, and thrombocytopenia. All of these syndromes include pancytopenia to some degree.

*Bone marrow aplasia*- is defined as a profound loss of bone marrow  
30 resulting in pancytopenia. Drugs known to cause bone marrow aplasia include, but are not limited to, chloramphenicol, gold salts, mephenytoin, penicillamine, phenylbutazone, and trimethadione. In general these drugs are not first line therapy due to the rare occurrence of marrow aplasia. Specific forms of aplasia include:

*Granulocytopenia*- is defined as a loss of polymorphonuclear neutrophils to a  
35 count lower than 500. Granulocytopenia primarily predisposes the patient to bacterial and fungal infections. Drugs known to cause granulocytopenia include, but are not limited to, captopril, cephalosporins, choral hydrate, chlorpropamide,

penicillins, phenothiazines, phenylbutazone, phenytoin, procainamide, propranolol, and tolbutamide.

*Aplastic anemia*- is a disorder involving an inability of the hematologic cells to regenerate and thus there is a dramatic depletion of one or more of the following cell types: neutrophils, platelets, or reticulocytes. Drugs associated with producing aplastic anemia are: 1) agents or compounds that produce bone marrow depression, for example cytotoxic drugs used in cancer chemotherapy; 2) agents or compounds that frequently, but inevitably, produce marrow aplasia, for example benzene; 3) agents or compounds that are associated with aplastic anemia, for example chloramphenicol, antiprotozoals, and sulfonamides.

Aplastic anemia is almost always a result of damage to the hematopoietic stem cells. There are two possible routes for the destruction of these cells: 1) direct damage to the stem cell DNA, and 2) cell cycle dependant depletion of later stage progenitor cells. In the first case, drugs or agents bind to and randomly damage the genetic material. This type of aplasia is associated with both early aplasia (immediate or direct cytotoxicity) or later myelodysplasia and leukemia. In the latter case, mitotically and metabolically active progenitor cells are preferentially affected and progenitor cell depletion may lead to unregulated proliferation of spared stem cells.

*Leukopenia*- is defined when the circulating peripheral white cell count falls below  $5-10 \times 10^9$  cells per liter. Circulating leukocytes consist of neutrophils, monocytes, basophils, eosinophils, and lymphocytes.

Neutropenia is defined when the peripheral neutrophil count falls below  $2 \times 10^9$  cells per liter. There are a number of drugs families that can cause neutropenia including, but not exclusive to, antiarrhythmics (procainamide, propranolol, quinidine), antibiotics (chloramphenicol, penicillins, sulfonamides, trimethoprim-methoxazole, para-aminosalicylic acid, rifampin, vancomycin, isoniazid, nitrofurantoin), antimalarials (dapson, quinine, pyrimethamine), anticonvulsants (phenytoin, mephénytoin, trimethadione, ethosuximide, carbamazepine), hypoglycemic agents (tolbutamide, chlorpropamide), antihistamines (cimetidine, brompheniramine, tripeleminamine), antihypertensives (methylopa, captopril), antiinflammatory agents (aminopyrine, phenylbutazone, gold salts, ibuprofen, indomethacin), diuretics (acetazolamide, hydrochlorothiazide, chlorthalidone), phenothiazines (chlorpromazine, promazine, prochlorperazine), antimetabolite immunosuppressive agents, cytotoxic agents (alkylating agents, antimetabolites, anthracyclines, vinca alkyls, cis-platinum, hydroxyurea, actinomycin D), and other agents (alpha and gamma interferon, allopurinol, ethanol, levamisole, penicillamine).

*Lymphoid hyperplasia*- is characterized by reactive changes within the T-cell regions of the lymph node that encroach on, and at times appear to efface, the germinal follicles. In these regions, the T-cells undergo progressive transformation to immunoblasts. These reactions are encountered particularly in response to drug-induced immunoreactivity. Drugs known to cause lymphoid hyperplasia are phenytoin, and mephenytoin.

*Hemolytic anemia*- is characterized by the premature destruction of red cells, accumulation of hemoglobin metabolic by-products, and a marked increase in erythropoiesis within the bone marrow. Drugs known to cause hemolytic anemia include, but are not excluded to, methyldopa, penicillin, sulfonamides, and vitamin E deficiency.

*Thrombocytopenia*- is characterized by a marked reduction in the number of circulating platelets to a level below 100,000/mm<sup>3</sup>. Drug-induced thrombocytopenia may result from decreased production of platelets or decreased platelet survival or both. Drugs known to cause thrombocytopenia include, but are not excluded to, ethanol, acetaminophen, acetazolamide, acetylsalicylic acid, 5-aminosalicylic acid, carbamazepine, chlorpheniramine, cimetidine, digitoxin, diltiazem, ethchlorvynol, gold salts, heparin, hydantoins, isoniazid, levodopa, meprobamate, methyldopa, penicillamine, phenylbutazone, procainamide, quinidine, quinine, ranitidine, Rauwolfia alkaloids, rifampin, sulfonamides, sulfonylureas, cytotoxic drugs, and thiazide diuretics.

## II. Impact of Stratification Based Upon Genotype in Drug Development for Drugs, Compounds, or Candidate Therapeutic Interventions that may Induce Blood Dyscrasias

Clozapine induced agranulocytosis is associated with differing HLA types and HSP70 variants in patients for whom responded to clozapine therapy but developed agranulocytosis. This is suggestive that a gene within the MHC region is associated with the manifestation of agranulocytosis in response to clozapine therapy. In a recent study, two ethnic groups were analyzed for genetic markers for the agranulocytosis. Tumor necrosis factor microsatellites d3 and b4 were found in higher frequencies in patients that experience clozapine-induced agranulocytosis. These data are suggestive that there is an involvement of tumor necrosis factor constellation polymorphism and clozapine-induced agranulocytosis.

There is evidence to suggest that there are safety response differences to drug therapy in reference to development of blood dyscrasias which may be attributable to genotypic differences between individuals. There is provided in this invention examples of gene pathways that are implicated in the disease process or its therapy and those that potentially cause this variability. The Detailed Description above

demonstrates how identification of a candidate gene or genes and gene pathways, stratification, clinical trial design, and implementation of genotyping for appropriate medical management of a given disease can be used to identify the genetic cause of variations in clinical response to therapy, new diagnostic tests, new therapeutic approaches for treating this disorder, and new pharmaceutical products or formulations for therapy. Gene pathways including, but not limited to, those that are outlined in the gene pathway Tables 1-6, preferably Table 3, and pathway matrix Table 8 and discussed below are candidates for the genetic analysis and product development using the methods described above.

Advantages of Inclusion of Pharmacogenetic Stratification in Clinical Development of Agents that May Cause Blood Dyscrasias

As an example of identification of the primary gene and relevant polymorphic variance that directly affects efficacy, safety, or both one could select an gene pathway as described in the Detailed Description, and determine the effect of genetic polymorphism and therapy efficacy, safety, or both within that given pathway. For example, referring to Table 8, genes involved in drug transport, phase I and phase II metabolism, protection from reactive intermediate damage, and immune responsiveness the optimization of therapy of by an agent known to have a blood dyscrasia side effect by determining whether the patient has a predisposing genotype in which the selected agents are more effective and or are more safe. In considering an optimization protocol, one could potentially predetermine the genotypic profile of these genes involved in the manifestation of the adverse effect, or those genes preeminently responsible for drug response. By embarking on the previously described gene pathway approach, it is technical feasibility to determine the relevant genes within such a targeted drug development program.

Example 18

Drug-Induced Toxicity: Cutaneous Toxicity

Drug-induced cutaneous toxicity includes, but is not excluded to, eczematous: photodermatitis (phototoxic and photoallergic), exfoliative dermatitis; maculopapular eruption; papulosquamous reactions: psoriaform, lichus planus, or pityriasis rosea-like; vesiculobullous reactions; txic epidermal necrolysis; pustular-acneform reactions; urticaria and erythemas: urticaria, erythema multiforme; nodular lesions: erythema nodosum, vasculitis reaction; telangiectatic and LE reactions; pigmentary reaction; other cutaneous reactions: fixed drug reactions, alopecia, hypertrichosis, macules, papules, angioedema, morbilliform-maculopapular rash, toxic epidermal necrolysis, erythema multiforme, erythema nodosum, contact

dermatitis, vesicles, petechiae, exfoliative dermatitis, fixed drug eruptions, and severe skin rash (Stevens-Johnson syndrome).

Drugs known to be associated with cutaneous toxicities include, but are not exclusive of, antineoplastic agents, sulfonamides, hydantoins and others listed for each type of toxicity.

*Urticaria and angioedema*- is defined as the transient appearance of elevated, erythematous pruritic wheals (hives) or serpiginous exanthem. The appearance of urticaria is perceived as ongoing immediate hypersensitivity reaction. Angioedema is defined as urticaria, but involving deeper dermal and subdermal sites. Urticaria and angioedema appear to result from dilation of local postcapillary venules. Degranulation of cutaneous mast cells may be involved.

Drugs associated with urticaria and angioedema include, but are not excluded to, antimicrobials include, but not exclusive of, 5-aminosalicylic acid, aminoglycosides, cephalosporins, ethambutol, isoniazid, metronidazole, miconazole, nalidixic acid, penicillins, quinine, rifampin, spectinomycin, sulfonamides, and other drugs: asparaginase, aspirin and other non-steroidal antiinflammatory agents, calcitonin, chloral hydrate, chlorambucil, cimetidine, cyclophosphamide, daunorubicin, ergotamine, ethchlorvynol, doxorubicin, ethosuximide, ethylenediamine, glucocorticoids, melphalan, penicillamine, phenothiazines, procainamide, procarbazine, quinidine, tartazine, thiazide diuretics, thiotepa.

*Morbilloform-maculopapular rash*- are rashes that result in eruptions or are morbilliform in nature.

Drugs associated with rashes include, but are not limited to, 5-aminosalicylic acid, cephalosporins, erythromycin, gentamicin, penicillins, streptomycin, sulfonamides, allopurinol, barbiturates, captopril, coumarin, gold salts, hydantoins, thiazide diuretics.

*Toxic epidermal necrolysis and erythroderma and exfoliative dermatitis*-

Cutaneous erythroderma, edema, scaling, and fissuring may occur in response to certain drugs. Drugs associated with these types of cutaneous reactions include, but are limited to, allopurinol, amikacin, captopril, carbamazepine, chloral hydrate, chlorambucil, chloroquine, chlorpromazine, cyclosporine, diltiazem, ethambutol, ethylenediamine, glutethimide, gold salts, griseofulvin, hydantoins, hydroxychloroquine, minoxidil, nifedipine, nonsteroid antiinflammatory agents, penicillin, phenobarbital, rifampin, spironolactone, sulfonamides, trimethadione, trimethoprim, tocainamide, tocainide, vancomycin, verpamil.

*Erythema multiforme*- is characterized by a hypersensitivity reaction in blood vessels of the dermis. The hypersensitivity is the result of immune complexes formed by small molecules interacting with proteinaceous components of the blood

vessels. In cases whereby the mucosal membranes of the mouth and eye are involved, is referred to as Stevens-Johnson syndrome. Typically the cutaneous lesions, blisters and painful erosions occur in the mouth and eye.

Drugs associated with erythema multiforme include, but are not limited to, allopurinol, acetaminophen, amikacin, barbiturates, carbamazepine, chloroquine, chlorpromazine, clindamycin, ethambutol, ethosuximide, gold salts, glucocorticoids, hydantoins, hydralazine, hydroxyurea, mechlorethamine, meclofenamate, penicillins, phenothiazides, phenolphthalein, phenylbutazone, rifampin, streptomycin, sulfonamides, sulfonyleureas, sulindac, vaccines.

#### *Fixed drug eruptions-*

Drugs associated with fixed drug eruptions include, but are not excluded to, acetaminophen, 5-aminosalicylic acid, aspirin, barbiturates, benzodiazepines, barbiturates, chloroquine, dapsone, dimethylhydrazine, gold salts, hydralazine, hyoscine, ibuprofen, iodides, meprobamate, methamphetamine, metronidazole, penicillins, phenobarbital, phenolphthalein, phenothiazides, phenylbutazone, procarbazine, pseudoephedrine, quinine, saccharin, streptomycin, sulfonamides, and tetracyclines.

*Erythema nodosum-* is an inflammatory reaction in subcutaneous fat which represents a hypersensitivity reaction to a number of antigenic stimuli. Multiple red, painful nodules do not ulcerate but involute and leave a yellow-purple bruises. Small molecules interacting with proteinaceous components form a sensitizing antigen.

Drugs associated with producing erythema nodosum include, but are not excluded to, bromides, oral contraceptives, penicillins, and sulfonamides.

*Contact dermatitis-* is characterized by eruptions on histological analysis to epidermal intercellular edema (spongiosis). Contact dermatitis can be caused by allergic or irritant mechanisms. Allergic contact dermatitis is a delayed hypersensitivity reaction that can occur in response to a variety of small molecules that when bound to proteinaceous components of the skin form a sensitizing antigen. The antigen is processed by Langerhans' cells in the epidermis, presenting the antigen to the circulating T lymphocytes. Irritant dermatitis is produced by substances that irritate or have a direct toxic effect on the skin.

Drugs associated with contact dermatitis side effects include, but are not limited to, ambroxol, amikacin, antihistamines, bacitracin, benzalkonium chloride, benzocaine, benzyl chloride, cetl alcohol, chloramphenicol, chlorpromazine, clioquinol, colophony, ethylenediamine, fluorouracil, formaldehyde, gentamycin, glucocorticoids, glutaraldehyde, heparin, hexachlorophene, iodochlorhydroxyquin, lanolin, local anesthetics, minoxidil, naftin, neimycin, nitrofurazone, opiates, para-

aminobenzoic acid, parabens, penicillins, phenothiazines, proflavine, propylene glycol, streptomycin, sulfonamides, thimerosal, timolol.

5 *Impact of Stratification Based Upon Genotype in Drug Development for Drugs, Compounds, or Candidate Therapeutic Interventions that May Induce Cutaneous Reactions*

10 Recently, it has been described that there is a deletion polymorphism in the B2 bradykinin receptor gene (B2BKR). It was revealed that there is a 9 base pair deletion in exon 1 of the B2BKR gene and upon inspection of patients experiencing angioedema, patients with immunochemical evidence of angioedema were homozygous for no deletion at that site. These results were suggestive of B2BKR genotype influence on the clinical status and manifestation angioedema.

15 There is evidence to suggest that there are safety response differences to drug therapy in reference to development of cutaneous reactions which may be attributable to genotypic differences between individuals. There is provided in this invention examples of gene pathways that are implicated in the disease process or its therapy and those that potentially cause this variability. The Detailed Description above demonstrates how identification of a candidate gene or genes and gene pathways, stratification, clinical trial design, and implementation of genotyping for appropriate medical management of a given disease can be used to identify the genetic cause of variations in clinical response to therapy, new diagnostic tests, new therapeutic approaches for treating this disorder, and new pharmaceutical products or formulations for therapy. Gene pathways including, but not limited to, those that are outlined in the gene pathway Tables 1-6, more preferably Table 3, and pathway matrix Table 8 and discussed below are candidates for the genetic analysis and product development using the methods described above.

25 Advantages of Inclusion of Pharmacogenetic Stratification in Clinical Development of Agents that May Cause Cutaneous Reactions

30 As an example of identification of the primary gene and relevant polymorphic variance that directly affects efficacy, safety, or both one could select an gene pathway as described in the Detailed Description, and determine the effect of genetic polymorphism and therapy efficacy, safety, or both within that given pathway. For example, referring to Table 8, genes involved in drug transport, phase I and phase II metabolism, protection from reactive intermediate damage, and immune responsiveness, the optimization of therapy of by an agent known to have a cutaneous side effect by determining whether the patient has a predisposing

genotype in which the selected agents are more effective and or are more safe. In considering an optimization protocol, one could potentially predetermine the genotypic profile of these genes involved in the manifestation of the adverse effect, or those genes preeminently responsible for drug response. By embarking on the previously described gene pathway approach, it is technically feasible to determine the relevant genes within such a targeted drug development program.

### **Example 19**

#### **Drug-Induced CNS Toxicity**

Drug-induced central nervous system toxicity includes CNS stimulation or CNS depression. Characteristics of CNS toxicity include, but are not limited to, tinnitus and dizziness, acute dystonic reactions, parkinsonian syndrome, coma, convulsions, depression and psychosis, sweating, mydriasis, hyperpyrexia, centrally mediated cardiovascular involvement (hypertension, tachycardia, extrasystoles, arrhythmias, circulatory collapse) and respiratory depression or tachypnea. Drugs known to be associated with CNS toxicity include, but are not exclusive of, salicylates, antipsychotics, sedatives, cholinergics,

#### ***Impact of Stratification Based Upon Genotype in Drug Development for Drugs, Compounds, or Candidate Therapeutic Interventions that May Induce CNS Toxicity***

There is evidence to suggest that there are safety response differences to drug therapy in reference to development of CNS toxicities which may be attributable to genotypic differences between individuals. There is provided in this invention examples of gene pathways that are implicated in the disease process or its therapy and those that potentially cause this variability. The Detailed Description above demonstrates how identification of a candidate gene or genes and gene pathways, stratification, clinical trial design, and implementation of genotyping for appropriate medical management of a given disease can be used to identify the genetic cause of variations in clinical response to therapy, new diagnostic tests, new therapeutic approaches for treating this undesirable adverse effect, and new pharmaceutical products or formulations for therapy. Gene pathways including, but not limited to, those that are outlined in the gene pathway Tables 1-6, more preferably Table 3, and pathway matrix Table 8 and discussed below are candidates for the genetic analysis and product development using the methods described above.

#### **Advantages of Inclusion of Pharmacogenetic Stratification in Clinical Development of Agents that May Cause CNS Toxicities**



As an example of identification of the primary gene and relevant polymorphic variance that directly affects efficacy, safety, or both one could select an gene pathway as described in the Detailed Description, and determine the effect of genetic polymorphism and therapy efficacy, safety, or both within that given pathway. For example, referring to Table 8, genes involved in drug transport, phase I and phase II metabolism, protection from reactive intermediate damage, the optimization of therapy of by an agent known to inpart CNS toxic or undesirable side effect or effects by determining whether the patient has a predisposing genotype in which the selected agents are more effective and or are more safe. In considering an optimization protocol, one could potentially predetermine the genotypic profile of these genes involved in the manifestation of the adverse effect, or those genes preeminently responsible for drug response. By embarking on the previously described gene pathway approach, it is technical feasibility to determine the relevant genes within such a targeted drug development program.

### **Example 20**

#### **Drug-Induced Liver Toxicity**

Drug-induced liver disease or drug-induced liver toxicity can manifest as zonal necrosis, nonspecific focal hepatitis, viral hepatitis-like reactions, inflammatory or noninflammatory cholestasis, small or large droplet fatty liver, granulomas, chronic hepatitis, fibrosis, tumors, or vascular lesions.

In the majority of the cases of known drug-induced liver toxicity, the drug is metabolized to a form that is deleterious to hepatic, or extrahepatic function. There are many endogenous or exogenous compounds that may be considered to attenuate or ablate toxic hepatocyte-produced metabolite mechanisms or effects of hepatic or extrahepatic damage.

In hepatocellular damage, free oxygen radicals may be generated in the hepatic metabolic processes that are deleterious to intracellular organelles, DNA, or metabolic pathways. There are endogenous cytoprotective agents that may prevent free radical-mediated damage such as retinoids, flavins, reduced glutathione, vitamin E, S-adenylylmethionine, and the enzyme superoxide dismutase (SOD). In animal models in which SOD activity is diminished or absent, the liver function was normal, but the sensitivity to toxin challenge was heightened.

In cholestatic damage, the bile salt uptake, metabolism, secretion, or transport is compromised and the residual increased bile salt concentrations are deleterious to hepatocyte function. The increase in bile salts is the main metabolic

disturbance that initially leads to jaundice and pruritis and can progress to pancreatitis, hyperbilirubinemia, biliary cirrhosis, and hepatic encephalopathy.

In both cases of drug-induced liver toxicity, the drug must first be absorbed and enter in the hepatic circulation. Further, clinically it is often difficult to determine whether cholestatic damage leads to hepatocellular damage or whether hepatocellular damage leads to cholestatic damage. In many cases, until the patient is symptomatic, the underlying damage mechanisms may be clinically overlooked. By the time the drug-induced liver disease is symptomatic, the damage, be it hepatocellular or cholestatic or both, may be irreversible.

#### *Identification of Genes involved in Drug-Induced Liver Toxicity*

Thus, in the process of identifying drug- or xenobiotic-induced liver toxicity, one skilled in the art would identify key metabolic enzymes or bile cannicula transport processes that would be linked with either hepatocellular damage or cholestasis or combination of hepatocellular damage or cholestasis.

Hepatocellular damage may be the result of direct chemical mediated effects, may be severe, and usually is associated with damage within organelles, DNA and membranes. Clinically there is a marked elevation of SGOT and SGPT as well as other enzymes. In cases of cholestasis there is jaundice, pruritis, a marked elevation of bile salts and alkaline phosphatase activity, but not an elevation of SGOT or SGPT. In cases of toxic liver disease there is difficulty, at least initially to determine the underlying etiology. Clinically, symptoms may not appear as clear as described above. Further, depending on the rate and extent of the damage, hepatocellular damage may be masked or asymptomatic until liver impairment has induced cholestasis.

Potentially hepatotoxic agents can be divided broadly into two groups: intrinsic hepatotoxins and idiosyncratic hepatotoxins. Intrinsic hepatotoxins produce acute liver damage in a predictable, dose-dependent fashion shortly after ingestion or exposure. Generally, all subjects exposed will uniformly exhibit signs and symptoms. In this category, the effects seen in humans can be mimicked in animal models. Examples of intrinsic hepatotoxins are carbon tetrachloride, 2-nitropropane, trichloroethane, the octapeptide toxins of the *Amanita* mushroom species, and the antipyretic, acetaminophen. In some of these cases, toxic metabolites result in covalent modification of hepatocyte macromolecules or reactive oxygen intermediates leads to peroxidation of cell membrane lipids or other intracellular molecules.

In contrast, idiosyncratic hepatotoxins produce liver damage in an unpredictable, dose-independent manner after a latent period of ingestion or

exposure. Animal models or experimental data is generally incapable of predicting the effect in humans. Further, idiosyncratic hepatotoxins do not uniformly affect a population; a subset of the group exposed may or may not exhibit signs or symptoms. Range of symptoms are from mild to severe and is thought to coincide with differences in the pathways of drug or xenobiotic biotransformation or immune-mediated drug sensitivity (drug allergy). In idiosyncratic drug-induced liver disease, fever, arthralgias, rash, eosinophilia, are often prominent and indicate a hypersensitivity reaction.

*Impact of Stratification Based Upon Genotype in Drug Development for Drugs, Compounds, or Candidate Therapeutic Interventions that may Induce Hepatotoxicity*

Genes encoding proteins with catalytic function that are involved in the metabolism of drugs or xenobiotics are listed in Tables 3 and 8 below. Further listed are those proteins that are involved in the uptake, transport, or secretion into the bile cannicula. Below are further specific example of drug-specific effects on the liver.

*Acetaminophen-Induced Liver Disease*

Acetaminophen is a readily available, easy to administer analgesic that is an example of a intrinsic hepatotoxin. This hepatotoxin causes zonal necrosis and acute liver failure and is associated with renal failure. Although a high dose (10-15 grams) is required for significant liver injury to occur, the onset of initial symptoms does not occur until hours after ingestion. The progression of symptoms occurs including progressive liver failure with hepatic encephalopathy, prolongation of prothrombin time, hypoglycemia, and lactic acidosis. The liver injury is caused by a toxic metabolite of acetaminophen via the P450 metabolizing system. This toxic intermediate at low concentrations is conjugated with glutathione. However, in toxic doses, the conjugating enzymes stores are exhausted and the reactive intermediate reacts with intracellular proteins and results in cellular dysfunction and ultimately death. The rate of metabolism is dependent on the concentrations of both P450 and glutathione. Speeding this toxic pathway may include increasing the available P450 or reducing the availability of glutathione, e.g. using known inducers of P450 such as ethanol and and phenobarbital; and known inhibitors of glutathione concentrations, e.g., ethanol and fasting. Acetaminophen toxicity is completely reversed if the drug is removed. Chronic ingestion may produce subclinical liver injury, centrilobular necrosis, or chronic hepatitis; however all reversible if the drug is removed.

*Amiodarone-Induced Liver Disease*

Amiodarone is used in treatment of refractory arrhythmias. In some patients amiodarone produces mild to moderate increases of serum transaminases which are generally accompanied by engorgement of lysosomes with phospholipid. In a fraction of the patients, a more severe liver injury develops which histologically resembles alcoholic hepatitis: fat infiltration of hepatocytes, focal necrosis, fibrosis, polymorphonuclear leukocyte infiltrates, and Mallory bodies. The lesion may progress to micronodular cirrhosis, with portal hypertension and liver failure. Hepatomegaly is seen, but jaundice is rare.

Amiodarone accumulates in lysosomes and inhibits lysosomal phospholipases, however the connection between this mechanism and alcoholic hepatitis histopathology is unknown. Unfortunately, rapid discontinuation of amiodarone increases the risk of cardiac arrhythmias.

#### *Chlorpromazine-Induced Liver Disease*

Chlorpromazine is an anti-psychotic agent which, in a small portion of the patient population can produce a cholestatic reaction. Symptoms include fever, anorexia, arthralgias, pruritis, jaundice, and eosinophilia is common. This idiosyncratic type of liver toxicity suggests a hypersensitivity type reaction. The symptoms subside over a period of weeks following discontinuation. Rarely, residual cholestatic disease occurs, treatment for pruritis and fat-soluble vitamin supplementation may be required, but eventual recovery almost always occurs.

#### *Erythromycin-Induced Liver Disease*

Erythromycin, a broad spectrum antibiotic, can be accompanied by a cholestatic reaction. Inflammatory cell infiltration and liver cell necrosis may occur. The hepatotoxicity presents as right upper quadrant pain, fever, and variable cholestatic symptoms. The prognosis is uniform and will occur after readministration of the drug. The mechanism of action is unknown.

#### *Halothane-Induced Liver Disease*

Halothane is a gaseous anesthetic and can, in rare instances, cause a viral-like hepatitis syndrome. In severe cases, this hepatotoxicity, may cause fatal massive hepatic necrosis. Severe reactions seem to appear after previous or multiple exposure to halothane. It is known that the P450 metabolites of this xenobiotic are responsible for the mechanism of hepatic injury.

#### *Isoniazid (INH)-Induced Liver Disease*

Isoniazid is used as a single drug in the prophylaxis of tuberculosis. In 10-20% of the persons taking INH, subclinical liver injury occurs. The conversion of INH to acetylhydrazine is via acetylation. In slow acetylators, INH is more hepatotoxic. The conversion of INH to acetylhydrazine to diacetylhydrazine is impaired. In slow acetylators, the acetylhydrazine is not well metabolized and is further oxidized by one of the P450 enzymes to a toxic, reactive molecule that is responsible for the liver disease. Discontinuation of the drug returns the enzymatic levels to normal and the liver is able to restore activity.

#### *Sodium Valproate-Induced Liver Disease*

Sodium valproate is an anti-epileptic agent that is routinely prescribed for petit mal epilepsy and in some cases produces severe hepatotoxicity. Similar to INH, sodium valproate is accompanied by a high incidence of transient, slight and asymptomatic increases in serum transaminases. Usually the increased enzyme activity appears after weeks of treatment. In rare cases of severe liver toxicity, the nonspecific systemic and digestive symptoms are followed by jaundice, evidence of liver failure, as well as encephalopathy and coagulopathy. The mechanism of hepatotoxicity is unknown, however there are theories that there is impairment of mitochondrial oxidation of long-chain fatty acids by a metabolite of the parent drug. Symptoms subside with little to no residual liver dysfunction after discontinuing the drug.

#### *Oral Contraceptive Induced Liver Disease*

Estrogen, progesterone, and combination oral contraceptives can produce several adverse effects on the hepatobiliary system. They are 1) hepatocellular cholestasis, 2) liver cell neoplasias, 3) increased predisposition to cholesterol and gall stone formation, 4) hepatic vein thrombosis. These cholestatic hepatotoxic effects are attributed to estrogen's direct effect on bile formation. The mechanism of action is unknown.

There is evidence to suggest that there are safety response differences to drug therapy in reference to development of drug-induced liver toxicity which may be attributable to genotypic differences between individuals. There is provided in this invention examples of gene pathways that are implicated in the disease process or its therapy and those that potentially cause this variability. The Detailed Description above demonstrates how identification of a candidate gene or genes and gene pathways, stratification, clinical trial design, and implementation of genotyping for appropriate medical management of a given disease can be used to identify the genetic cause of variations in clinical response to therapy, new diagnostic tests, new

therapeutic approaches for treating this disorder, and new pharmaceutical products or formulations for therapy. Gene pathways including, but not limited to, those that are outlined in the gene pathway Tables 1-6, more preferably Table 3, and pathway matrix Table 8 and discussed below are candidates for the genetic analysis and product development using the methods described above.

Advantages of Inclusion of Pharmacogenetic Stratification in Clinical Development of Agents that May Cause Liver Toxicity

As an example of identification of the primary gene and relevant polymorphic variance that directly affects efficacy, safety, or both one could select an gene pathway as described in the Detailed Description, and determine the effect of genetic polymorphism and therapy efficacy, safety, or both within that given pathway. For example, referring to Table 8, genes involved in drug transport, phase I and phase II metabolism, excretion, hepatic cannicular uptake and concentration, and protection from reactive intermediate damage the optimization of therapy by an agent known to have a hepatic side effect by determining whether the patient has a predisposing genotype in which the selected agents are more effective and or are more safe. In considering an optimization protocol, one could potentially predetermine the genotypic profile of these genes involved in the manifestation of the adverse effect, or those genes preeminently responsible for drug response. By embarking on the previously described gene pathway approach, it is technical feasibility to determine the relevant genes within such a targeted drug development program.

Example 21

Drug-Induced Cardiovascular Toxicity

Drug induced cardiovascular toxicities include but are not excluded to arrhythmias, tachycardia, extrasystoles, circulatory collapse, QT prolongation, cardiomyopathy, hypotension, or hypertension. Drugs known to elicit these type of responses include but are not excluded to theophylline, hydantoins, doxorubicin, daunorubicin.

Arrhythmias-If the normal sequence of electrical impulse and propagation through myocardial tissue is perturbed, an arrhythmia occurs. Broadly, arrhythmias fall into one of three categories: bradyarrhythmias (slowing or failure of the initiating impulse), heart block (an impaired propagation through node tissue or atrial or ventricular muscle), and tachyarrhythmias (abnormal rapid heart rhythms).

Subcategories include: sinus bradycardia, atrioventricular block (AV block), sinus tachycardia, ventricular tachycardia, atrial flutter, multifocal atrial tachycardia, polymorphic ventricular tachycardia with or without QT prolongation, frequent or

difficult to terminate ventricular tachycardia, atrial tachycardia with or without AV block, ventricular bigeminy, and ventricular fibrillation. Drugs known to induce these types of arrhythmias include, but are not excluded to, digitalis, verapamil, diltiazem, b-adrenergic blockers, clonidine, methyldopa, quinidine, flecainide, propafenone, theophylline, sotalol, procainamide, disopyramide, certain non-cardioactive drugs ( ), and amiodarone.

Heart Rate, Tachycardia-Heart rate is under both sympathetic and parasympathetic control. The influence of heart rate on cardiac output is paramount. Drugs affecting heart rate include, but are not limited to, sympathomimetics, parasympathomimetics, and agents or compounds affecting these two central inputs.

Extrasystoles- is defined as premature myocardial excitation. Extrasystoles can include atrial, nodal, or ventricular. Other asynchronous pathologies may result from these systoles. Drugs known to be associated with extra systoles include, but are not excluded to, agents that prolong the depolarization time, agents that leave a residual available intracellular calcium, or agents that alter the function of the K<sup>+</sup> or Na<sup>+</sup> channel activity.

QT Prolongation- is the interval on an electrocardiogram that indicates ventricular action potential duration. QT prolongation can lead to uncoordinated atrial and ventricular action potentials. In these circumstances of delayed or prolonged polymorphic ventricular afterdepolarizations, resultant abnormal triggering of secondary, uncoordinated depolarizations can occur. Two of these conditions are explained as follows and may be associated with underlying rapid or slow heart rate: 1) under conditions of residual excess intracellular calcium (myocardial ischemia, adrenergic stress, digitalis intoxication), and 2) under conditions of marked prolongation of cardiac action potential (agents (antiarrhythmics or others) that prolong action potential duration).

Cardiomyopathy-There are broadly three categories of cardiomyopathies: dilated, hypertrophic, and restrictive. These cardiac muscular diseases can be of mechanical or acquired origin.

Dilated cardiomyopathies are generally caused by myocardial injury that results in depressed systolic function and progressive ventricular dilatation. Drug induced dilated cardiomyopathy can occur in the presence of, but are not excluded to, ethanol, chemotherapeutic agents, elemental compounds, and catecholamimetics.

Hypertrophic cardiomyopathy is the presentation of grossly asymmetric (eccentric) or symmetric (concentric) hypertrophy of the left ventricle in the absence of another cardiac or systemic disease capable of producing the disproportionate increase in ventricle mass. In drug induced hypertrophic cardiomyopathy, there may be compensatory hypertrophy of the left ventricle in response to inordinate and or

sustained hypertension or prolonged reduced or insufficient cardiac output as a result of myocardial injury or noncardiac mediated physiological events.

Restrictive cardiomyopathies are the result of a primary abnormality of diastolic function (impaired filling). Impaired diastolic function can occur as a result of morphologically detectable myocardial or endomyocardial disease, interstitial deposition of abnormal substances (infiltrative), intracellular accumulation of abnormal substances (storage diseases), or as a result of endomyocardial disease. In the last category, anthracyclines have been associated with both dilated and restrictive cardiomyopathies.

Blood Pressure-Blood pressure is regulated in a complex interplay of neural and endocrine mechanisms. These mechanisms are aimed at the physiologic control of cardiac output, delivery of blood components to the tissues, and removal of metabolic by-products from the tissues.

Hypertension is defined as the elevated arterial blood pressure either an increase of systolic or diastolic pressure or both. Secondary hypertension can be associated with drugs and chemicals including, but not limited to, cyclosporine, oral contraceptives, glucocorticoids, mineralocorticoids, sympathomimetics, tyramine, and MAO inhibitors.

Hypotension is defined as the reduction in blood pressure that is associated with orthostatic hypotension, syncope, head injury, hepatic failure, antidiuresis, myocardial infarction and cardiogenic shock. Drug-induced hypotension is associated drugs including, but not exclusive of, parasympathomimetics, diuretics, and direct acting cardiac agents.

#### Advantages of Inclusion of Pharmacogenetic Stratification in Clinical Development of Agents that May Cause Cardiovascular Toxicity

As an example of identification of the primary gene and relevant polymorphic variance that directly affects efficacy, safety, or both one could select an gene pathway as described in the Detailed Description, and determine the effect of genetic polymorphism and therapy efficacy, safety, or both within that given pathway. For example, referring to Table 8, genes involved in drug transport, phase I and phase II metabolism, and protection from reactive intermediate damage the optimization of therapy of by an agent known to have a cardiovascular side effect by determining whether the patient has a predisposing genotype in which the selected agents are more effective and or are more safe. In considering an optimization protocol, one could potentially predetermine the genotypic profile of these genes involved in the manifestation of the adverse effect, or those genes preeminently



responsible for drug response. By embarking on the previously described gene pathway approach, it is technical feasibility to determine the relevant genes within such a targeted drug development program.

## **Example 22**

### **Drug-Induced Pulmonary Toxicity**

Drug induced pulmonary toxicity includes, but is not excluded to, asthma, acute pneumonitis, eosinophilic pneumonitis, fibrotic and pleural reactions, and interstitial fibrosis. Drug known to elicit pulmonary toxicity include, but are not excluded to, salicylates, nitrofurantoin, busulfan, nitrofurantoin, and bleomycin.

### **Advantages of Inclusion of Pharmacogenetic Stratification in Clinical Development of Agents that May Cause Pulmonary Toxicities**

As an example of identification of the primary gene and relevant polymorphic variance that directly affects efficacy, safety, or both one could select an gene pathway as described in the Detailed Description, and determine the effect of genetic polymorphism and therapy efficacy, safety, or both within that given pathway. For example, referring to Table 8, genes involved in drug transport, phase I and phase II metabolism, excretion, protection from reactive intermediate damage, and immune responsiveness, the optimization of therapy of by an agent known to have a pulmonary side effect by determining whether the patient has a predisposing genotype in which the selected agents are more effective and or are more safe. In considering an optimization protocol, one could potentially predetermine the genotypic profile of these genes involved in the manifestation of the adverse effect, or those genes preeminently responsible for drug response. By embarking on the previously described gene pathway approach, it is technical feasibility to determine the relevant genes within such a targeted drug development program.

## **Example 24**

### **Drug-Induced Renal Toxicity**

Drug-induced renal toxicity includes, but is not excluded to, glomerulonephritis and tubular necrosis. Drugs associated with eliciting renal toxicity include, but are not excluded to, penicillamine, aminoglycoside antibiotics, cyclosporine, amphotericin B, phenacetin, and salicylates.

### **Advantages of Inclusion of Pharmacogenetic Stratification in Clinical Development of Agents that May Cause or are Associated with Renal Toxicity**

As an example of identification of the primary gene and relevant polymorphic variance that directly affects efficacy, safety, or both one could select an gene pathway as described in the Detailed Description, and determine the effect of genetic polymorphism and therapy efficacy, safety, or both within that given pathway. For example, referring to Table 8, genes involved in drug transport, phase I and phase II metabolism, and renal tubular uptake and concentration the optimization of therapy of by an agent known to have a renal side effect by determining whether the patient has a predisposing genotype in which the selected agents are more effective and or are more safe. In considering an optimization protocol, one could potentially predetermine the genotypic profile of these genes involved in the manifestation of the adverse effect, or those genes preeminently responsible for drug response. By embarking on the previously described gene pathway approach, it is technical feasibility to determine the relevant genes within such a targeted drug development program.

#### **Example 24**

##### **Asthma**

##### ***I. Description of Asthma***

Asthma can be an acute or chronic condition associated with inflammation of the lower airways and variable levels of airflow obstruction. Asthma symptoms vary among individuals and may include wheezing, shortness of breadth, tightness of the chest, trouble controlling a cough, persistent cough at night, difficulty breathing during or soon after physical exertion or exercise, or waking up at night due to one of these symptoms. Episodes of these symptoms (referred to as asthma attacks, flare-ups, or exacerbations) occur when there is sufficiently severe airway constriction to render a patient almost unable or unable to breathe. There can be warning signs , however, many attacks are sudden and unanticipated.

Individuals with asthma have inflamed airways that are supersensitive to inducers of asthma which exacerbate asthma and enhance underlying inflammation such as allergens, respiratory infections, or industrial pollutants. Provokers of asthma leading to bronchospasm include exercise or physical activities, irritants, emotions and aspirin. Asthma attacks are associated with swollen and inflamed linings of the airways, excess mucus in the airways, and bronchospasm which are reversible. In chronic asthma, there is persistent activation of resident cells (e.g. basophils, eosinophils, neutrophils) lining the airway leading to chronic inflammation which can result in irreversible changes in the airway pasages. These permanent changes are part of a remodeling process.

Recent evidence has suggested that airway inflammation is a major factor in the pathogenesis and in the severity of the disease. One theory holds that asthma is a T helper 2 (Th2) cell-driven chronic eosinophilia mediated via dendritic and other antigen-presenting cells. The inflammatory nature of the disease is multicellular in nature, with mast cells, eosinophils, macrophages, basophils, lymphocytes, neutrophils, and epithelial cells participating and therefore immunoglobulins, cytokines, chemokines, adhesion molecules, proteinases, inflammatory mediators, and growth factors are involved in various stages and interact to maintain and amplify the inflammatory response. The net result of these interactions is persistent inflammation and repair, ultimately leading to irreversible airway remodeling.

## *II. Current therapies for Asthma*

Because asthma results from a complex combination of mediators of inflammation, most useful anti-asthma agents affect pathways for these mediators. In acute or chronic asthma, the therapeutic categories include: immunosuppressive agents including glucocorticoids, antiinflammatory agents including leukotriene receptor agonists and mast cell stabilizers (cromolyn sulfate); bronchodilators including  $\beta$ -adrenergic agonists, sympathomimetic agents, and xanthines; and agents to treat cough and excess mucus including expectorants and mucolytics.

Corticosteroids affect the inflammation within the airways by decreasing growth and development of mast cells, inducing apoptosis, suppressing lymphocyte generation of IL-5 and other cytokines, inhibiting some mediator release, inhibiting cytokine production, inhibiting the transcription of cytokines (for example IL-8, TNF- $\alpha$ , prototypic antiviral chemokine (regulated-on-activation normal T-expressed and secreted, RANTES), and GM-CSF), and inhibiting nitric oxide synthesis.

$\beta$ -Adrenergic agonists and sympathomimetics affect the pulmonary airway lining in a well-characterized mechanism of  $\beta$ -adrenergic receptor activation of adenylyl cyclase as well as cAMP independent mechanisms. Bronchodilation is the immediate clinical effect.

Leukotriene modifiers affect the airway by inhibition of 5-lipoxygenase, the initial enzyme of leukotriene biosynthesis, and exert their effect by decreasing leukotriene production, thereby interfering with eosinophil migration and other processes.

Corticosteroids affect the inflammation within the airways by decreasing growth and development of mast cells, inducing apoptosis, suppressing lymphocyte generation of IL-5 and other cytokines, inhibiting some mediator release, inhibiting cytokine production, inhibiting the transcription of cytokines (for example IL-8,

TNF- $\alpha$ , prototypic antiviral chemokine (regulated-on-activation normal T-expressed and secreted, RANTES), and GM-CSF), and inhibiting nitric oxide synthesis.

Corticosteroids in combination with long-acting  $\beta$ -adrenergic agonists work well as combination therapy.

5 Cromones are believed to act on the airway by modifying mediator release, and inhibiting mast cell degranulation.

Xanthines are believed to act on the airway in asthma by inhibiting eosinophil cell migration, and enhancing  $\beta$ -adrenergic pathway mediated bronchodilation via the inhibition of phosphodiesterase.

10 Difficult to treat or therapy-resistant asthma syndromes present a challenge to clinicians. They include difficult acute and chronic, as well as chronic severe, acute severe, therapy-resistant, difficult to control and corticosteroid-dependent asthma.

### 15 *III. Limitations of Current Therapies for Asthma*

#### Limitations Involving Efficacy

The therapies discussed above do not reverse the underlying pathological process in asthma; they merely slow or retard the progression of asthma. As thickening of the airways occurs and becomes irreversible the therapeutic options  
20 become limited. Thus, therapies for asthma are aimed at reduction of inflammatory processes and control of symptoms starting at the earliest date (frequently in the pediatric setting).

The limitations of the adrenergic agonist compounds used for the treatment of asthma include short duration of action and ligand desensitization. Excessive use of  
25 short acting  $\beta$ -adrenergic agonists has been proposed to lead to loss of asthma control and consequent increases in morbidity and mortality. Long acting bronchoactive/bronchoprotective agonists acting at adrenergic receptors have supplanted short duration  $\beta$ -agonists.

30 Short-acting  $\beta$ -adrenergic agonists are primarily used for the relief of acute asthma symptoms. Excessive reliance on these agents is generally not advisable because 1)  $\beta$ -adrenergic receptors undergo a rapid desensitization and the agonist becomes an ineffective bronchodilator, and 2) repetitive high doses of short acting  $\beta$ -adrenergic agonists may be detrimental to the control of asthma by potentially interfering with corticosteroid action. This desensitization occurs through a process  
35 involving G-protein receptor coupled-kinases and or cAMP dependent protein kinase or by enhanced degradation of cAMP by phosphodiesterase activity.

Glucocorticoid associated side effects include increased appetite, weight gain, fluid retention, acne, ecchymosis, development of Cushingoid facies,

hypertension, hyperkalemia, diabetes, hyperglycemia, hyperosmolar state, hyperlipidemia, hepatic steatosis, atherosclerosis, myopathy, aseptic necrosis, osteoporosis, ulcers, pancreatitis, psuedotumor cerebri, psychosis, glaucoma, cataract formation, vascular necrosis, increased suseptibility to infection, impairment of the hypothalamus-pituitary axis, decreased thyroid hormone serum binding protiens, and impaired wound healing.

Theophylline or other phosphodiesterase inhibitors have been shown to have a narrow therapeutic window and can result in life-threatening cardiac arrhythmias.

Difficult to treat asthma involves a spectrum of disease that responds suboptimally to doses of glucocorticoids. In the face of partial response to inhaled or oral steroids, higher doses are administered risking steroid associated side-effects.

The reduction of clinical symptoms of asthma following antiinflammatory therapy may only become evident after several weeks to months of therapy. The slow action of these therapies creates problems for the clinician seeking to expeditiously determine optimal therapy for an individual patient. The development of genetic tests to predict response to different agents will allow selection of optimal therapy with less of the time consuming empirical clinical decision making required presently.

#### Limitations Involving Toxicity or Undesired Side Effects

There are toxicities and undesired side effects associated with the above current therapies for asthma that require monitoring. Drugs used to treat asthma may cause death, disability, disease, and place a fetus at risk. The undesired side effects or toxicities are listed for each drug category as described above.

#### *IV. Impact of Stratification Based Upon Genotype in Drug Development for Drugs, Compounds, or Candidate Therapeutic Interventions for Asthma*

In a recent report, it was demonstrated that the 5-lipoxygenase (5-LO) gene promoter variation among asthma patients is linked to drug response to 5-LO inhibitors (Drazen et al., Nature Genetics 22: 1999). In a clinical trial to test efficacy of a potent, selective 5-LO inhibitor (ABT-761), the trial was abruptly closed due to inordinate event rate of abnormal liver function tests. Although the projected enrollment was not reached, the interim data suggested superior efficacy regarding forced expiratory volume in the high dose relative to low dose or placebo groups. The investigators chose to stratify the high dose and placebo group of the enrolled patients based upon genotype of the 5-LO gene promoter. The 5-LO gene promoter has been found to contain 3-6 tandem repeats of the Sp1-binding motif. The wild-type allele was designated as 5 tandem repeats and had a frequency of

0.772 in the study population. The forced expiratory volume data indicated that heterozygous patients on high-dose active treatment had, on average, an improvement of forced expiratory volume within one week ( $23.3 \pm 6.0\%$ ) and was similar to the wild-type patients ( $18.8 \pm 3.6\%$ ). In contrast, the patients with mutant genotype had no benefit from active 5-LO inhibitor treatment ( $-1.2 \pm 2.9\%$ ). In the table below, the trial outcome data is described for two periods following treatment with high dose or placebo.

| Patient Group        | FEV <sub>1</sub> , % change from baseline <sup>a</sup> |        |
|----------------------|--------------------------------------------------------|--------|
|                      | Day 8                                                  | Day 84 |
| Wild type, high dose | 8.2                                                    | 18.5   |
| Mutant, high dose    | 1.8                                                    | 5      |
| Placebo              | -0.7                                                   | -1.4   |

<sup>a</sup>Data extrapolated from published data

Approximately 6% of asthma patients do not carry a wild-type allele at the 5-LO core promoter locus, and this data indicates that these patients would not benefit from 5-LO inhibitor drug therapy. Further, these data indicate that there is evidence to reasonably identify patients, i.e. stratification based upon 5-LO genotype, to appropriately treat patients with asthma.

A recent double blind, placebo controlled crossover designed pharmacogenetic retrospective clinical trial of a  $\beta$ 2-adrenoreceptor polymorphism was implemented to analyze the significance of  $\beta$ 2-adrenoreceptor polymorphisms (Tan et al. Lancet 350:995-999). *In vitro* studies have suggested that polymorphism of the  $\beta$ 2-adrenergic receptor may influence the desensitization induced by  $\beta$ 2 agonists. Twenty two moderately severe asthmatics were enrolled into a placebo controlled cross-over study of formoterol (a  $\beta$ 2-adrenergic agonist). The patients were divided into groups by allelic variances: 1) at codon 16, homozygous arginine (n=4), heterozygous arginine/glycine (n=8), and homozygous glycine (n=10); and 2) at codon 27, homozygous glutamine (n=5), heterozygous glutamine/glutamic acid (n=11), and homozygous glutamic acid (n=6). Genotypic analysis determined that individuals who were homozygous for glycine at codon 16 were also homozygous for glutamic acid at codon 27. The results were as follows:

| Polymorphisms of the $\beta$ 2-adrenergic | Degree of Brochodilator Desensitisation after Formoterol Therapy <sup>1</sup> |                           |                             |          |
|-------------------------------------------|-------------------------------------------------------------------------------|---------------------------|-----------------------------|----------|
|                                           | 6 hour FEV <sub>1</sub>                                                       | Maxim al FEV <sub>1</sub> | 6 Hour FEF <sub>25-75</sub> | Maxim al |

| receptor                 |     |     |      | FEF <sub>25-75</sub> |
|--------------------------|-----|-----|------|----------------------|
| Gly 16 (n=10)            | 80% | 48% | 103% | 73%                  |
| Arg 16 (n=4)             | 28% | -8% | 23%  | -35%                 |
| Gly/Arg16 (n=8)          | 57% | 48% | 70%  | 50%                  |
|                          |     |     |      |                      |
| Glu27 (n=6) <sup>2</sup> | 73% | 35% | 90%  | 68%                  |
| Gln27 (n=5)              | 47% | 3%  | 38%  | -15%                 |
| Glu/Gln27 (n=11)         | 65% | 52% | 70%  | 45%                  |

<sup>1</sup>Data extrapolated from published graphs.

<sup>2</sup>All individuals homozygous for Glu27 were also homozygous for Gly16.

The homozygous glycine at position 16 was associated with individuals who were prone to bronchodilator desensitization than at arginine at position 16: the mean FEV<sub>1</sub> desensitisation was 80% for Gly16 homozygotes versus 28% for the Arg16 homozygotes. Similar results were observed for the 6 hour FEV<sub>1</sub> and the FEF.

For the polymorphism at codon 27, the mean for the Glu27 homozygous individuals demonstrated greater desensitization than those who were homozygous for Gln27.

The allelic variance, glycine at position 16 appeared to dominate over the putative protective effects of the mutation of glutamic acid at position 27.

The effects of the codon 16 and 27 polymorphism in the  $\beta$ 2-adrenoreceptor on  $\beta$ 2-agonist desensitization, as observed in the above data, suggest that there may be an identifiable subset of patients for whom  $\beta$ 2-adrenergic receptor desensitization occurs in the presence of long-acting or repeated use of  $\beta$ 2-agonists.

Thus, one skilled in the art, will be able to utilize the presently described pharmacogenetic techniques to identify the allelic variances with the coding region of the  $\beta$  -adrenergic receptor or other receptor proteins that are similar to the  $\beta$  -adrenergic receptor, including but not limited to those variances for those genes listed in Tables 4, 15, and 21 and those 7-membrane spanning receptor G-protein coupled receptors. In this way, a skilled practitioner will be able to utilize the methods, protocols, and techniques that are described in the detailed description and those known in the art to identify the gene targets, allelic variance or variances, and candidate drugs that affect these pathways. Further, one can design and implement a strategy that incorporates a diagnostic test to genotype the individual for a given allele or alleles or haplotype, grouping these candidates by genotype, and testing a  $\beta$ -adrenergic agonist or other candidate therapeutic product for the affect of the pharmacogenomic difference between or among the groups.

As described above, there is evidence to suggest that there are safety response differences to drug therapy in asthma which may be attributable to genotypic differences between individuals. There is provided in this invention examples of gene pathways that are implicated in the disease process or its therapy and those that potentially cause this variability. The Detailed Description above demonstrates how identification of a candidate gene or genes and gene pathways, stratification, clinical trial design, and implementation of genotyping for appropriate medical management of a given disease can be used to identify the genetic cause of variations in clinical response to therapy, new diagnostic tests, new therapeutic approaches for treating this disorder, and new pharmaceutical products or formulations for therapy. Gene pathways including, but not limited to, those that are outlined in the gene pathway Tables 1-6, preferably Table 4, and pathway matrix Table 9 and discussed below are candidates for the genetic analysis and product development using the methods described above.

As an example of identification of the primary gene and relevant polymorphic variance that directly affects efficacy, safety, or both one could select an gene pathway as described in the Detailed Description, and determine the effect of genetic polymorphism and therapy efficacy, safety, or both within that given pathway. For example, referring to Table 9, genes involved in cytokine-mediated immune regulation, non-cytokine mediated immune regulation (including, but not excluded to, cyclophilins, corticosteroids), cell mediated inflammation involving apoptosis, adhesion and migration, protease and protease inhibitors, complement, degranulation (platelets, mast cells, neutrophils, and eosinophils), release of inflammatory modulators (including membrane lipids, prostaglandin, platelet activating factor, leukotrienes, histamine, nitric oxide), vascularization mediators (including endothelin and vascular endothelial cell growth factor), neurotransmitters and peptide hormone inflammation modulators (including adrenergic, purinergic, cholinergic, ion channels, tachykinin, neurokinin, substance P, bradykinin, parathyroid hormone, melanocortin and adrenocorticotrophic hormones, and modulators of general cell growth pathways the optimization of therapy of by an agent can be achieved by determining whether the patient has a predisposing genotype in which the selected agents are more effective and or are more safe. In considering an optimization protocol, one could potentially predetermine the genotypic profile of these genes involved in the manifestation of the adverse effect, or those genes preeminently responsible for drug response. By embarking on the previously described gene pathway approach, it is technical feasibility to determine the relevant genes within such a targeted drug development program.



*Description of Mechanism of Action Hypotheses for Future Drug Development*

There are many potential mechanisms that may serve as targets for candidate therapeutic interventions. For example, phosphodiesterase inhibitors to PDE4; T-lymphocyte-eosinophil interactions inhibition: targeting the factors involved in the regulation of the TH2(CD+4) differentiation and/or activation by soluble factors (cytokines (IL-4, IL-5); co-stimulatory molecules (B7-2/CD86); and transcription factors (GATA-3, AP-1). These targets may be available to limit the TH2 cell involvement in the initiation of asthmatic inflammation.

Suppression of eosinophil adhesion with consequent inhibition of influx into the lung is a strategy to suppress asthmatic airway inflammation. Such inhibition may be mediated through inhibitors directed towards very late antigen-4 (VLA-4), monoclonal antibodies directed towards VLA-4, intracellular adhesion molecule 1 (ICAM1), and alpha 1,3-fucosyltransferase VII (an enzyme which regulates selectin function). Furthermore, molecules may be targeted to suppress the expression of adhesion molecules (e-selectin, vascular cell-adhesion molecule 1 (VCAM-1), and ICAM1).

There are a group of chemokines that contain a cysteine-X-cysteine motif, such as IL-8 that are effectors of acute inflammatory episodes, whereas cysteine-cysteine chemokines, such as macrophage inhibitory peptide 1 (MIP-1), eotaxin, RANTES, or macrophage chemotactic peptide 1 (MCP-1) act as chronic mediators of inflammation. These molecules may be appropriate targets for inhibiting either the acute or chronic inflammatory pathway.

Cysteinyl leukotrienes have a central role in the development of chronic asthma, and antagonists (i.e., CysLT<sub>1</sub>) may be able to ablate the actions of this ligand. These novel leukotriene receptor agonists may have potential for anti-inflammatory effects. Endothelin receptors may also be a target, with endothelin antagonists to specific receptor subtypes ET<sub>A</sub> or ET<sub>B</sub>. Other receptors known to be involved in the inflammatory process that may be potential targets are the tachykinin NK1 receptors and selective ligands to the NK1/NK2 receptors.

Induction of cyclooxygenase and the consequent increase in prostaglandin release is associated with the development of inflammation. Antisense oligonucleotides directed against the receptor types NK-kB, major basic protein, 5-lipoxygenase, leukotriene C4(LTC4 synthetase, IL-4, IL-5, IL-8 and adenosine have been developed that are inhalable products that can directly block the expression of these mediators of the inflammatory response.

Other areas of drug target development include immunobiology of the airways i.e., TH1 and TH2 and their involvement in the immune response, synthesis of immunoglobulin, IgE, integrins, inhibition of  $\alpha$ IL5 and  $\alpha$ IL5 monoclonal

antibody, soluble IL4 receptor, neurokinin receptor antagonist, chemokine inhibitors.

5 The inflammatory response is also being evaluated in terms of the effects of NO<sub>2</sub>, SO<sub>2</sub>, and ozone on the subsequent effect on airway response to these potential allergens. As well as adhesion molecule expression, cytokine production, and cytokine gene transcription factors.

10 Optimization of nonsteroidal or steroidal antiinflammatory agents, or agents aimed at a mechanism of therapy of the underlying etiology of asthma further demonstrates the utility of selection of a potential asthma patient that has a predisposing genotype in which selective antiasthmatic or other agents may be more effective and or have an more desirable safety profile. In considering an optimization protocol, one could potentially predetermine variance or variances within the nonsteroidal antiinflammatory pathway, steroid antiinflammatory pathway, or antiinflammatory mediated intracellular mechanism of action that is preeminently responsible for antiasthmatic drug response. By embarking on the previously described gene pathway approach, it is technically feasible to determine the relevant genes within such a targeted drug development program for asthma.

15 A sample of therapies approved or in development for preventing or treating the progression of asthma currently known in the art is shown in Table 47. In this table, the candidate therapeutics were sorted and listed by mechanism of action. Further, the product name, the pharmacologic mechanism of action, chemical name (if specified), and the indication is listed as well.

### **Example 25**

#### **Inflammatory Bowel Disease**

##### **Description of Inflammatory Bowel Disease**

25 Inflammatory bowel disease (IBD) is a broad clinical term that includes idiopathic chronic inflammatory bowel diseases including Crohn's disease (CD) and ulcerative colitis (UC) which can be distinguished from inflammatory bowel disease of known origin including diverticulitis, radiation enteritis, colitis, drug or toxin-induced enterocolitis, or vasculitis of the intestinal tract. UC is a term that encompasses a broad category of diffuse, continuous, and superficial inflammation of the colon, which begins within the rectum and extends proximally. The condition is limited to the colon and large intestine, with limited involvement of the small intestine. In UC, the inflammation primarily affects the mucosal process and is not transluminal within these anatomical regions. CD is characterized by focal, asymetric, transmural inflammation affecting any portion of the gastrointestinal tract, i.e. from the mouth to the anus. The focal localization and possible extent of the

inflammation distinguishes UC from CD. There are currently approximately 35-100 and 10-100 CD per 100,000 Americans diagnosed with UC or CD, respectively.

Clinically, patients with UC experience variable stool consistencies from constipation to diarrhea, low-grade fever, malaise, nausea, vomiting associated with defecation, night sweats, arthralgias, dehydration, tachycardia, and symptoms of abdominal tenderness. There can be rectal bleeding, tenismus, and passage of mucopus.

Patients with Crohn's disease experience symptoms of peptic ulcer disease, nausea, vomiting, and epigastric pain. Transmural inflammation leads to fibrosis and transluminal narrowing. In some cases, the narrowing leads to signs and symptoms of intestinal obstruction including nausea, vomiting, waves of abdominal pain, and a reduced output of stool. Patients with colonic CD are likely to experience abdominal pain, cramping or localized pain, rectal bleeding, and diarrhea. Weight loss is common among CD patients due to malabsorption of nutrients and reduced food intake due to minimization of postprandial symptoms.

There are extraintestinal manifestations of inflammatory bowel disease affecting the following processes including: nutritional and metabolic abnormalities, hematologic abnormalities, skin and mucous membranes, musculoskeletal, hepatic and biliary abnormalities, renal complications, and optic complications. These complications are associated when the colon or intestinal tract is inflamed. These complications are clinically manifested as joint swelling or pain, erythema nodosum, pyoderma gangrenosum, sclerosing cholangitis, conjunctivitis, or uveitis.

There is an increased risk for the development of gastrointestinal cancer in patients with IBD. In both UC and CD, there is an increased risk of adenocarcinoma of the intestine. This is not correlated to the intensity of the first attack, subsequent course, or and specific medical therapeutic approach. Therefore routine screening for dysplasia and neoplasia is warranted.

#### Current Therapy of Inflammatory Bowel Disease

Strategies for the therapy of inflammatory bowel disease includes antiinflammatory agents, and immunomodulation.

Antiinflammatory agents include the use of glucocorticoids and the aminosalicylates. Glucocorticoids act by modulation of the immune response. Corticosteroids affect the inflammation within the gastrointestinal tract by decreasing growth and development of mast cells, inducing apoptosis, suppressing lymphocyte generation of IL-5 and other cytokines, inhibiting some mediator release, inhibiting cytokine production, inhibiting the transcription of cytokines (for example IL-8, TNF- $\alpha$ , prototypic antiviral chemokine (regulated-on-activation

normal T-expressed and secreted, RANTES), and GM-CSF), and inhibiting nitric oxide synthesis.

5-aminosalicylic acid (5ASA) is a salicylate that is used for the treatment of IBD, is not orally active, is poorly absorbed and is inactivated by intestinal bacteria, and is delivered as a suppository or rectal suspension enema. Oral formulations can be used to deliver active drug to the lower intestine which are cogeners of 5ASA. The aminosalicylates are potent antiinflammatory agents that inhibit cyclooxygenase (COX), a rate limiting enzyme in the prostaglandin and leukotriene pathway.

Immunosuppressive agents are also used to modulate the inflammatory/immune response. There are four broad categories of immunosuppressive agents that have distinct mechanisms of action: inhibition of ribonucleotide synthesis which acts to inhibit the proliferation of T-cell clones (6-mercaptopurine), inhibition of folic acid which acts to inhibit T-cell and B-cell function as well as decrease IL-1 and IL-6 activity (methotrexate), inhibition of T-cell receptor stimulated transcription of lymphokine genes which act to inhibit the production of IL-2 and IL-2 receptors as well as inhibit certain cytokines (TNF- $\alpha$ , IFN- $\gamma$ ) (cyclosporin and FK506), and inhibition of guanosine nucleotide synthesis which acts as cytostatic effects on lymphocytes (mycophenolate). Each of these categories of agents have been employed for the therapy of IBD.

Recently a chimeric monoclonal antibody was approved for use in the treatment of moderately to severe active Crohn's disease for those patients that are unresponsive to conventional therapy. This monoclonal antibody is specific for TNF- $\alpha$  and can remove TNF from the bloodstream before it reaches the site of inflammation.

Crohn's disease may progress to a level and extent in which surgical removal of the localized inflammation is warranted. Surgery has been indicated for recurrent intestinal obstruction, complicated fistulas, intractable hemorrhage, disease refractory to medical therapy, growth retardation refractory to therapies, or cancer. The surgical procedures vary from excision of a localized, diseased portion of the gastrointestinal tract to removal of large portions, i.e. the entire colon (colectomy). Surgical excision of the inflamed region or to correct complications such as blockage, perforation, abscess, or bleeding can result in a substantial relief of symptoms.

#### Limitations to Current Therapies for IBD

Salicylate associated side effects include dyspepsia, gastric or small bowel bleeding, ulceration, renal insufficiency, confusion, rash, headache, hepatic toxicity. NSAIDs also reversibly inhibit platelet aggregation and prolong bleeding time.

Glucocorticoid associated side effects include increased appetite, weight gain, fluid retention, acne, ecchymosis, development of cushoid facies, hypertension, hyperkalemia, diabetes, hyperglycemia, hyperosmolar state, hyperlipidemia, hepatic steatosis, atherosclerosis, myopathy, aseptic necrosis, osteoporosis, ulcers, pancreatitis, psuedotumor cerebri, psychosis, glaucoma, cataract formation, vascular necrosis, increased susceptibility to infection, impairment of the hypothalamus-pituitary axis, decreased thyroid hormone serum binding proteins, and impaired wound healing.

Agents involved in immunomodulation have the following undesirable side effects including antimetabolites: hepatic compromise including hepatic fibrosis, ascites, esophageal varices, cirrhosis, pneumonitis, myelosuppression; immunosuppressives: myelosuppression, (cyclosporine: renal insufficiency anemia, hypertension.

Monoclonal antibody to TNF proteins therapies have been shown to generate a human-antimouse antibody response (HAMA). However, patients on immunosuppressive agents such as glucocorticoids and others are less likely to generate antibodies to the treatment antibody. Delayed hypersensitivity is demonstrable 2 to 4 years after initial treatment in 25% of the patients treated with the chimeric antibody. Further, there are patients that develop a serum sickness reaction which includes fever, and joint swelling that requiring hospital admission. A positive antinuclear antibody (ANA) occurred in 24-36% of the patients analyzed. Nine percent of the patients developed anti-DNA antibodies, less than 1% developed a lupus-like reaction requiring steroid therapy.

In surgical therapy of IBD, recurring inflammation and relapse, after excision procedures occurs in 75% of the patients. Attempts have been made to include salicylate therapy after resective surgery, however, the inflammation recurrence rate in that group was 52%.

Impact of Stratification Based Upon Genotype in Drug Development for Drugs, Compounds, or Candidate Therapeutic Interventions for Autoimmune Disease Thiopurine methyltransferase (TPMT)

The thiopurine S-methyltransferase (TPMT) is a cytosolic enzyme whose precise physiological role is unknown. This enzyme catalyzes the S-methylation of widely used immunosuppressive or cytotoxic thiopurine drugs such as 6-thioguanine, 6-mercaptopurine and azathioprine.<sup>8</sup> The *in vivo* activity of this cytosolic enzyme is characterized by interindividual and interethnic variability caused by the genetic polymorphism of the TPMT gene, which was discovered, using pharmacogenetic techniques, by the existence of three major phenotypes, high

(HM), intermediate (IM) and deficient (DM) methylation. As a consequence, individuals greatly differ in detoxication of thiopurine drugs to 6-methylmercaptopurine as well as the occurrence of side effects or therapeutic efficacy. Using genomic techniques, PCR-SSCP (polymerase chain reaction – single strand conformation polymorphism), Spire-Vayron de la Moureyre et al. 9 have defined the mutational and allelic spectrum of TPMT in a group of 191 Europeans. In this analysis, PCR-SSCP techniques identified allelic variances in the entire coding sequence, the exon-intron boundaries, the promoter region and the 3'-flanking region of the genes. Six mutations were detected throughout the ten exons and seven TPMT alleles were characterized. Within the promoter region, six alleles corresponding to a variable number of repeats (VNTR) were identified. The TPMT phenotype was correctly predicted by genotyping for 87% of individuals. A clear negative correlation between the total number of repeats from both alleles and the TPMT activity level was observed, indicating that VNTRs contribute to inter-individual variations of TPMT activity. This VNTR polymorphism can be considered responsible for shifts to lower or higher TPMT activities observed among discordant individuals. Seven out of the nine phenotyped HMs but genotyped IMs were carrier of a total of eight VNTR repeats. This low number of repeat can account for the switch to high TPMT activities of these samples.

One in 300 patients with IBD are homozygous-deficient for TPMT. The clinical relevance for this deficiency is that TPMT is the enzyme responsible for the conversion of 6-MP to 6-MMP, and the AZA compounds to 6-TG. In TPMT deficient patients, higher levels of 6-TG and 6-MMP are then produced and are associated with significant leukopenia. In general, patients produce variable levels of 6-TG and 6-MMP as determined by their intrinsic enzyme systems. Higher 6-TG levels are correlated with good therapeutic response, but produce leukopenia. Higher 6-MMP levels correlate with hepatotoxicity and in recent studies with leukopenia.

There is evidence to suggest that there are safety response differences to drug therapy in IBD which may be attributable to genotypic differences between individuals, one example being the TPMT gene described above. There is provided in this invention examples of other gene pathways that are implicated in the disease process or its therapy and those that potentially cause this variability. The Detailed Description above demonstrates how identification of a candidate gene or genes and gene pathways, stratification, clinical trial design, and implementation of genotyping for appropriate medical management of a given disease can be used to identify the genetic cause of variations in clinical response to therapy, new diagnostic tests, new therapeutic approaches for treating this disorder, and new pharmaceutical products

or formulations for therapy. Gene pathways including, but not limited to, those that are outlined in the gene pathway Tables 1-6, preferably Table 4, and Table 9 and discussed below are candidates for the genetic analysis and product development using the methods described above.

5  
V. *Description of Mechanism of Action Hypotheses for Future Drug Development*

The majority of the hypotheses for future therapeutic interventions for inflammatory bowel disease are based upon the understanding the immunologic mechanisms that cause and perpetuate the inflammation within the gastrointestinal tract. Although the initiating event is elusive, the resulting immunologic events have been studied. All of the gastrointestinal enterocytes have immunologic function. Under physiologic conditions, these enterocytes selectively activate CD8+ nonspecific suppressor cells, in response to inflammation. In patients with IBD, these enterocytes selectively stimulate the development of CD4+ helper T cells which can respond in two ways 1) the Th1 response which involves the activation of IL-2 and IFN-g and leads to delayed hypersensitivity and cellular immunity and 2) the Th2 response which involves IL-4, IL-5, IL-6, and IL-10 and leads to antibody response and humoral immunity. Both Th1 and Th2 responses are genetically controlled and are coordinately regulated, i.e. Th1 response stimulation results in down regulation of Th2 response and vice versa. It has been demonstrated that in UC patients the Th2 response is favored and in CD patients the Th1 response is favored.

25 A humanized (95% human, 5% mouse) version of the chimeric antibody (75% human, 25% mouse) to TNF is currently under development. Some antiidiotypic antibodies are generated, but it doesn't appear to stimulate a delayed hypersensitivity, no stimulation of anti-DNA antibodies, or lupus-like reactions.

Mediators of the immune response including intracellular adhesion molecule (ICAM-1) inhibitors (antisense molecules or others), IL-10, IL-11 have been tested in humans. Further, and anti-CD4 monoclonal antibody which has been shown to interfere with the interaction of the CD4 molecule and the HLA class II molecules leading to an inhibition of antigen presentation has been tested.

Thalidomide (inhibitor of TNF, acceleration of the degradation of the TNF mRNA) is also under consideration.

35 It has been noted that individuals who smoke tobacco products have a lower incidence of IBD. Therefore, understanding the immune response and correlation with nicotinic chloinerbic pathways is under investigation.

A sample of therapies approved or in development for preventing or treating the progression of IBD currently known in the art is shown in Table 48. In this table, the candidate therapeutics were sorted and listed by mechanism of action. Further, the product name, the pharmacologic mechanism of action, chemical name (if specified), and the indication is listed as well.

### **Example**

#### **Hepatitis C**

#### **Selecting Optimal Therapy for HCV Patients**

#### **Genetically Determined Variation in Response to Interferon $\alpha$**

Treatment of hepatitis C virus (HCV) infection with interferon  $\alpha$  is expensive, benefits a minority of patients, and produces side effects in a significant fraction of patients. Addition of ribavirin increases efficacy, but combination therapy remains expensive and still falls well short of providing a lasting benefit to most patients. It would therefore be desirable to identify prospectively those patients likely to have a sustained response to treatment. Ideally a diagnostic test would also predict what dose of interferon and ribavirin, administered for what length of time, will afford to each patient the best chance of a sustained response. Pre-treatment identification of patients likely to suffer serious toxic side effects would also be desirable.

The best characterized predictors of response to interferon  $\alpha$  therapy are viral load and HCV genotype. Low viral load before therapy is predictive of a positive response. However, demonstration of decreased viral load after initiation of therapy is currently the best predictor of response to therapy. There is no consensus on the optimal time after initiation of therapy for measuring viral levels; periods ranging from 2 weeks to four months have been proposed. The viral load test is not very effective at discriminating long term responders from those patients who suffer rebound of HCV infection within 6 months after treatment. Also, the ideal test would be performed in advance of any treatment, thereby saving the considerable costs associated with even short term therapy. In search of other predictive indices, over 100 controlled clinical studies have examined a variety of viral and host factors in responders and nonresponders. Genetic variation in both HCV and host genes has been shown to independently influence patient response to interferon  $\alpha$  treatment. A consensus has emerged regarding the interaction of viral genotype and treatment response, however the contribution of host factors to treatment response has not been as well investigated. There are a number of promising recent findings suggesting that polymorphisms in regulators of human immune function are correlated with response to interferon  $\alpha$ .



### Viral genome variation

Comparison of sequenced HCV genomes reveals considerable variation in viral sequence, with at least 6 major types and well over a dozen minor types recognized. The geographical distribution of viral types is nonrandom, perhaps accounting for some of the apparent racial heterogeneity in the natural history of HCV infection. HCV is present in each patient as a heterogeneous population of viral quasispecies, with the degree of heterogeneity differing among patients. Despite these complexities, there are strong correlations between predominant viral type and treatment response. In general, patients with genotype 1 (especially 1b) respond poorly to interferon  $\alpha$ , with many studies showing response rates under 10 percent. Patients with genotype 2 or 3 do well, with response rates typically greater than 40 percent. Most viral genotyping is based on a short variable segment, however there are multiple segments of the viral genome that vary, and some studies have found that more detailed viral genotyping, for example of the 5' untranslated region, provides stronger correlations with treatment response.

### Human genome variation

A recent study suggests that there is significant variation in response to interferon  $\alpha$  treatment among racial groups in the US, even after controlling for the effect of different HCV types. This finding suggests that host genetic variation may be an important factor in response. A number of candidate genes have recently been tested for correlation with interferon  $\alpha$  response. The best studied genes are regulators of immune function such as IL-6, IL-10 and TNF $\alpha$ . One study, for example, found that patients with high expression of IL-10 (attributable to a specific haplotype) tend to respond poorly to interferon, perhaps due to impaired immune response. IL-4, IL-12 and TGF- $\beta$  levels have been correlated with treatment response in some (but not all) studies, however no genetic analysis has been performed. Similarly, hepatic levels of interferon  $\alpha$ - $\beta$  receptor have been correlated with response to interferon, but no genetic analysis has been performed to determine whether polymorphism affects receptor levels. HLA alleles have also been correlated with response to interferon, particularly the A24-B54-DR2 haplotype. A number of other compelling candidate genes have not been investigated. For example, a recent report shows that HCV can enter cells via the low density lipoprotein receptor. If so, the well studied amino acid polymorphisms of the LDL-R should be investigated for effects on disease course and response to treatment. There are also likely to be genetic factors that influence response to ribavirin; for example, the drug must be transported across the plasma membrane and then

phosphorylated before becoming a substrate for viral enzymes. The transporters and kinases responsible for these processes may be worth genetic investigation.

An optimal test for selecting treatment for HCV infection would (i) suggest the optimal therapeutic regimen (interferon alone, interferon and ribavirin, or some other combination), (ii) suggest the optimal dose and duration of treatment, (iii) predict sustained responders vs. short term responders, and (iv) predict patients likely to suffer serious adverse effects. At least three areas should be further investigated to better predict the response to interferon  $\alpha$  treatment. First, it is not clear that conventional viral genotyping methods, focusing on the 5' untranslated region, capture all of the aspects of viral sequence variation that affect viral biology. Additional genetic determinants of viral pathogenicity should be investigated. Second, the human gene variants that have been associated with response need to be more thoroughly investigated, and interactions between human candidate gene alleles, as well as perhaps between human genes and viral genes, should be tested. Third, recent work suggests a number of new host proteins that may affect response to interferon, and proteins that mediate response to ribavirin have not yet been investigated. The genes encoding these proteins should be thoroughly investigated. With additional information on candidate genes available it should be possible to construct a plan, ideally via retrospective analysis of clinical trial data, for first assessing the impact of variation in each of the candidate genes, then examining gene x gene interactions, and finally reducing the number of tests to a much smaller number for confirmatory prospective trials.

In Table 49, there a list of the candidate therapeutic interventions that in development for Hepatitis. One skilled in the art could apply, as described in the text, the methods of this invention to ascertain whether there is a gene in the inflammatory pathway that may be involved in the efficacy, safety, or toxicities of these candidate interventions.

### **Example 27**

#### **Pro12Ala Substitution in PPAR $\gamma$ 2 Affects Insulin Sensitivity**

Peroxisome proliferator-activated receptors (PPARs) are members of the nuclear hormone receptor family of DNA binding transcription factors. PPARs form heterodimers with retinoid X receptors and the resultant heterodimers, in coordination with coactivators and corepressors, bind to DNA and activate transcription of various genes. The PPAR superfamily includes receptors that mediate the size and number of peroxisomes in response to a diverse group of chemicals both naturally occurring and xenobiotics. Endogenous ligands thought to activate the PPARs are arachidonic acid, oleic acids, andogenous molecules (fatty

acids or steroids), C18 unsaturated fatty acids, peroxisome proliferation activators, and others (see Table 5). Diverse chemicals can activate the PPARs: herbicides, leukotriene antagonists, plasticizers (phthalate ester plasticizers used in the production of vinyl plastics), the fibrate class of hypolipidemic agents, thiazolidinediones. Overstimulation of these receptors can result in hepatomegaly, liver hyperplasia, and possibly hepatocellular carcinoma. There are three known PPARs,  $\alpha$ ,  $\gamma$ ,  $\delta$ . PPAR $\alpha$  is believed to be involved in the regulation and control of fatty acid oxidation enzymes. PPAR $\alpha$  is has been shown to have high expression rates in heart, adipose, and liver. PPAR $\gamma$  is believed to be involved in adipocyte differentiation. PPAR $\gamma$  is expressed in high levels in adipocyte tissues. PPAR $\delta$  (NUC1) is believed to be involved in a family of DNA binding proteins that are involved in adipogenesis and may be involved in early development. PPAR $\delta$  has been has been shown to have high expression in heart, kidney, and lung.

PPAR $\alpha$  is involved in the metabolic control of the expression of genes encoding fatty acid oxidation enzymes. Data from several experimental strategies have supported the hypothesis of the mechanism of action of PPAR $\alpha$ : 1) PPAR $\alpha$  is necessary for the induction of peroxisomal biogenesis in response to peroxisomal proliferating agents; 2) the target genes of PPARs are enzymes involved in cellular fatty acid oxidation which include mitochondrial, peroxisomal, and cytochrome P450 pathways; 3) PPAR $\alpha$  is activated by fatty acids or inhibitors of mitochondrial long-chain fatty acid import. It has been shown that PPAR $\alpha$  modulates the expression of genes encoding lipid metabolism enzymes, lipid transporters, or apolipoproteins. In an animal model of hyperlipidemia, activators of PPAR $\alpha$  was shown to decrease the lipid production in hepatocytes, however PPAR $\alpha$  activation also demonstrated tumor promotion within the same animals. Ligands that can specifically activate the lipostat enzymes while not turning on tumor production would be advantageous.

PPAR $\gamma$  is thought to be involved in the differentiation of preadipocytes to adipocytes. Overexpression of PPAR $\gamma$  in a non-adipose cell, i.e. nonadipogenic fibroblasts, results in the conversion to fat-laden adipocyte-like cells after exposure to a PPAR $\gamma$  ligand. Another transcription factor family involved in adipogenesis is the CAAT/enhance binding protein, CEBP. CEBP $\alpha$  is expressed in high abundance in adipose tissue and may play a direct role in establishing and maintaining the fully differentiated adipocyte phenotype. This hypothesis is based mainly on the data that indicates CEBP $\alpha$  is expressed late in adipogenesis and after key enzymes are induced. In other studies it has been shown that PPAR $\gamma$  and CEBP $\alpha$  expression can both be induced by CEBP $\beta$  and CEBP $\delta$ . PPAR $\gamma$  and CEBP $\alpha$  both induce the

expression of each other as well as activate and maintain the adipocyte proliferative and growth differentiation program.

The PPAR $\gamma$  gene has two transcription start sites and translation results in two distinct proteins PPAR $\gamma$ 1 and PPAR $\gamma$ 2. Both are highly expressed in adipose tissue. As in other nuclear hormone receptors, PPAR $\gamma$  is dependent on ligand activation. Currently, known biological ligands are 15-deoxy- $\Delta^{12,14}$  prostaglandin J, other prostanoids, and products from the linoleic acid pathway, i.e. oxLDL, HETE, 13-HODE and 9-HODE. Xenobiotics from the thiazolidinedione group, i.e. troglitazone, ciglitazone, and pioglitazone can directly activate PPAR $\gamma$ .

Modulation of PPR activities are thought to be effective strategies for the development of products for therapy of cancers (breast, prostate, and acute promyleocytic leukemia), metabolic diseases including thyroid disease and diabetes mellitus. PPAR $\gamma$  is expressed at significant levels in human primary and metastatic breast adenocarcinomas. Experimental evidence has suggested that the PPAR $\gamma$  transcriptional pathway can induce terminal differentiation of malignant breast epithelial cells. Ligands known to activate PPAR $\gamma$  have been shown to cause lipid accumulation, reduction of growth rate, and a reversion to a differentiated, less malignant state in studies of cultured breast cancer cells. Further, inhibition of MAP kinase, a negative regulator of PPAR $\gamma$ , enhances the activation by a PPAR $\gamma$  ligand (i.e. thiazolidinedione) sensitivity.

In studies of an animal model of diabetes, ligands that specifically activate PPAR $\gamma$  (i.e. troglitazone), normalization of elevated glucose levels in obese animals was demonstrated. Studies have been conducted to ascertain the efficacy of thiazolidinediones to treat NIDDM. One product troglitazone (Rizulin) has achieved approval for human therapeutic use in the U.S.

In a recent study, it was determined whether genetic variation in the PPAR $\gamma$  coding region was associated with obesity and insulin sensitivity or resistance, as well as type II diabetes mellitus (Deeb et al., Nature Genetics, 1998). It was determined that there was a single polynucleotide base substitution (C/G) which lead  
5 to a substitution in the coding sequence of proline to alanine at amino acid position 12 (Pro12Ala). The study included two human populations, Finns and Japanese-Americans. It was determined that the relative frequency of the the alanine allele frequency in the Finn study population (nondiabetic, including some with impaired glucose tolerance) was 0.12 whereas the Japanese-American frequency was 0.022 in  
10 type II DM patients, 0.039 in patients with impaired glucose tolerance, and 0.093 in normal subjects. In both populations there was an association of the Ala allele frequency and lower fasting insulin levels and body mass index, as well as higher insulin sensitivity; in the Finn population the values achieved statistical significance.

The study further demonstrated a functional correlation of the population  
15 data with in vitro PPAR $\gamma$  transcription factor binding affinities. In these experiments, it was shown that the Ala-isoform demonstrated a two- to five-fold decrease in relative affinity for the identified peroxisome proliferator response element, as well as a 36% faster off rate in comparison with the values detected for the PPAR $\gamma$  Pro isoform. Confirmatory data in the form of reduced detectable  
20 transactivation by the PPAR $\gamma$  ligand in the case of the PPAR $\gamma$  Ala isoform.

In addition, there is data to suggest that PPAR $\gamma$  mRNA expression levels are reduced in obese individuals and that the the ratio of mRNA encoding PPAR $\gamma$  is positively correlated with body mass index.

These data suggest that there is an association of reduced transcription  
25 activation by the Ala PPAR $\gamma$  allelic variant. Further suggesting, that there is a molecular mechanism for the observed body mass index and insulin sensitivity in the individuals having these allele polymorphisms. The data reported suggests that via reduced transcription of target genes that are involved in regulation of glucose homeostasis.

### **Example 28**

#### **Sulfonylurea receptor silent polymorphism and insulin levels**

In a sub-population that is approximately three times more likely to acquire  
35 type II DM, Mexican-Americans have higher insulin concentrations, and are more likely to exhibit insulin resistance. It has further been determined that in this population of Americans, hypeinsulinemia is a risk factor for the development of type II DM.

The high affinity sulfonylurea receptor (SUR1) is known to be involved in the regulation of insulin secretion. This receptor may be involved in type II DM. The SUR1 gene product is a functional part of the pancreatic  $\beta$ -cell KATP ion channel. The channel complex is composed of a two subunits, the sulfonylurea binding domain and the  $\beta$ -cell KATP channel responsible for conducting an inward rectifying potassium current. With the  $\beta$ -cell, metabolism of glucose produces changes in the relative concentrations of ADP and ATP which leads to a reduction of the KATP channel activation, causing a depolarization of the  $\beta$ -cell membrane and exocytosis of insulin. Within the nucleotide-binding fold region (NBF) of the SUR1, mutations have been shown to be autosomal recessive and lead to clinical familial hyper insulinemia. Other mutations in the SUR1 have been associated with Beckwith-Waldemann-syndrome associated malignant insulinomas.

In exon 31, there is a silent polymorphism (AGG/AGA) that encodes an arginine residue at position 1272. In the Mexican American study population that had the AGA genotype, there were higher fasting and 2 hr. insulin levels as well as a higher proinsulin to insulin ratio than those observed in the wild-type genotype subgroup. Between the two groups there were similar values for fasting glucose, body mass index, and waist circumference measurements.

| Test Parameter           | AGA   | AGG   | P value |
|--------------------------|-------|-------|---------|
| Fasting insulin*         | 113.4 | 82.8  | 0.043   |
| 2 hr. insulin*           | 849.6 | 498.6 | 0.0003  |
| Proinsulin/insulin ratio | 0.068 | 0.056 | 0.030   |

\*values in pmol/l

These data taken together suggests that there is an association between the SUR1 allelic variant and hyperinsulinemia in normal individuals from a high DM risk ethnic group.

### **Example 29**

#### **Vitamin D Receptor and Estrogen Receptor Polymorphisms and Response to Hormone Replacement Therapy**

Bone mineral density (BMD), a predictor of risk of bone fractures, decreases rapidly in postmenopausal women. Hormone replacement therapy (estrogen) reduces the rate of or prevents the decrease in BMD. Genetic factors contribute to 60-80% of BMD variation. In a recent study (Deng et al., Hum Genet 103:576-585), it was shown that hormone receptor polymorphisms affect BMD in elderly women

and that genotype should be considered when prescribing hormone replacement therapy (HRT) to preserve bone mass in elderly Caucasian women.

A population of 108 women participated in the study. They were genotyped for polymorphic differences in their vitamin D (VDR) and estrogen (ER) receptors. Using restriction endonuclease specific sites within these genes, it was determined that the VDR has a polymorphic *BsmI* site (B or b) and the ER has two polymorphic sites, *XbaI* (X or x) and *PvuII* (P or p). In the placebo and HRT groups, the VDR and ER genotype groups had significant affect on the BMD measurements. An analysis of the gene-by-gene interaction revealed that the level of significance was reduced. The amount of variation in BMD attributable to the VDR and ER polymorphisms varied from approximately 1% (for the total body bone mineral content changes in the placebo or HRT groups) to approximately 18.7% (for the spine bone mineral density changes occurring in the HRT group). Significant genotype effects were observed in the xx, PP, or bb groups having a larger decrease of bone mass during the study period, whereas a genotype of XX, pp, or BB is associated with smaller decreases (or larger increase) of bone mass.

This study demonstrates and interaction of drug response with genotype with age/reproductive status.

### **Example 30**

#### **Cholesterol ethyl-transferase (CETP)**

A well studied polymorphism in the first intron of the gene encoding cholesterol ester transfer protein (CETP) provides an example of a polymorphism in the non-coding region of a gene that has with an impact on drug efficacy via a recessive genetic mechanism.

The high-density lipoprotein (HDL) cholesterol concentration is inversely related to the risk of coronary artery disease. CETP has a central role in the metabolism of HDL and may therefore alter the susceptibility to atherosclerosis. The DNA of 807 men with angiographically documented coronary atherosclerosis was analyzed for the presence of a polymorphism in the gene coding for CETP. The presence of a DNA variation in a *Taq I* restriction enzyme site was referred to as B1, and its absence as B2. All patients participated in a cholesterol-lowering trial of the drug pravastatin designed to reduce cholesterol synthesis by inhibiting HMGCoA Reductase, and thereby arrest progression of, or induce the regression of coronary atherosclerosis and were randomly assigned to treatment with either pravastatin or placebo for two years. The B1 variant of the CETP gene was associated with both higher plasma CETP concentrations (mean [ $\pm$ SD],  $2.29 \pm 0.62$   $\mu$ g per milliliter for the B1B1 genotype vs.  $1.76 \pm 0.51$   $\mu$ g per milliliter for the B2B2 genotype) and lower

HDL cholesterol concentrations ( $34 \pm 8$  vs.  $39 \pm 10$  mg per deciliter). In addition, a significant dose-dependent association between CETP genotype and the progression of coronary atherosclerosis in the placebo group (decrease in mean luminal diameter:  $0.14 \pm 0.21$  mm for the B1B1 genotype,  $0.10 \pm 0.20$  mm for the B1B2 genotype, and  $0.05 \pm 0.22$  mm for the B2B2 genotype). This association was abolished by pravastatin. Pravastatin therapy slowed the progression of coronary atherosclerosis in B1B1 carriers but not in B2B2 carriers (representing 16 percent of the patients taking pravastatin). There was a significant interaction between pravastatin treatment and decreases in the mean luminal diameter ( $P = 0.01$ ) and the minimal luminal diameter ( $P = 0.05$ ). The association of the B1 allele with greater progression of diffuse atherosclerosis (i.e., greater decreases in the mean luminal diameter), as observed in the placebo group, was influenced by the use of pravastatin. In fact, the B1 allele appeared to be associated with less progression in the patients who were receiving pravastatin.

There was a co-dominant relation between the B1 allele and the efficacy of pravastatin in retarding the progression of coronary atherosclerosis. Carriers of two B1 alleles benefited most from treatment with pravastatin: they had significantly less progression of coronary atherosclerosis, as evidenced by smaller decreases in both the mean luminal diameter ( $P = 0.001$ ) and the minimal luminal diameter ( $P = 0.002$ ), than their B1B1 counterparts in the placebo group. Furthermore, carriers of only one B1 allele (B1B2) who were receiving pravastatin had significantly less focal atherosclerosis ( $P = 0.01$ ) than their counterparts in the placebo group. Finally, B2B2 homozygotes had a nonsignificantly greater progression at the end of the study than their counterparts in the placebo group.

Both the association of the CETP TaqIB genotype with the decrease in either the mean luminal diameter or the minimal luminal diameter in the placebo group and the interaction between the genotype and pravastatin treatment remained significant after adjustments were made for the mean luminal diameter (or minimal luminal diameter) at base line, the base-line HDL cholesterol concentration, changes in HDL cholesterol concentrations, and activities of both hepatic lipase and lipoprotein lipase. The precise molecular mechanism that underlies the relation between the CETP gene variant and the angiographic response to pravastatin treatment cannot be deduced from this study. However, it may be related to plasma concentrations of CETP.

The observations suggest that high CETP concentrations, and therefore high levels of CETP activity, result in an enhanced transfer of cholesteryl esters to atherogenic lipoproteins and have negative effects on the structure and function of



the HDL pool, which increases the risk of coronary artery disease. This inference is in agreement with the observation that the pravastatin-induced reduction in CETP concentrations was associated with beneficial angiographic effects in patients who had high CETP concentrations -- that is, those who were homozygous for the B1 allele. In contrast, the reduction in CETP concentrations induced by pravastatin in patients with genetically determined low plasma concentrations of CETP -- that is, those who were homozygous for the B2 allele -- was associated with a lack of retardation of the progression of coronary atherosclerosis. On the basis of these results and the finding of an increased risk of coronary artery disease in subjects who are heterozygous for CETP deficiency, it is believed that a critical concentration of CETP is required for normal reverse cholesterol transport. In contrast, high plasma concentrations of CETP, as seen in placebo-treated B1B1 patients, may promote atherosclerosis by increasing the cholesterol component of atherogenic lipoproteins.

One skilled in the art can apply the knowledge of the CETP allelic differences by applying the techniques as described in the detailed summary section. In this way, one could identify the known allelic differences as described above to identify other allelic differences within the CETP gene. One would then be able to utilize molecular biological techniques to provide a diagnostic test to identify the genotypic differences within a selected group of volunteers or patients. In this way, using the methods for designing and implementing a clinical study described in the detailed description, one could implement a clinical trial to further test the significance of allelic variances on the response to pravastatin, other statins, other cholesterol lowering drugs or other candidate drugs that are known to interact with or affect the CETP gene pathway.

### **Example 31**

#### **Angiotensin converting enzyme (ACE)**

The ACE polymorphism provides an example of a variance in the non-coding region of a gene with an impact on drug efficacy.

Angiotensin-converting enzyme (ACE) inhibitors, initially developed as antihypertensives, have been shown to reduce mortality in trials of patients with both symptomatic and asymptomatic left ventricular dysfunction and after acute myocardial infarction. An insertion/deletion polymorphism, consisting of a 287-base pair Alu repeat sequence, in intron 16 of the ACE gene, has been shown to predict approximately half of the variance in serum ACE levels between individuals. Homozygotes for the deletion allele (DD) have serum ACE levels twice as high on average as those homozygous for the insertion allele (II), whereas heterozygous (ID)

have intermediate levels. It has been demonstrated that genotype continues to predict residual ACE activity even after acute ACE inhibition with enalapril (Todd et al. Br J Clin Pharmacol 1995; 39:131-4). In a typical pharmacogenetic phase I design, comparing two groups of homozygotes healthy males, DD (n=12) and II (n=11) after genotyping 200 healthy normotensive men, the effect of enalapril, an ACE inhibitor drug, was significantly greater and lasted longer in the men homozygous for the II ACE genotype (Ueda et al. Circulation 1998; 98:2148-2153 ).

### **Example 32**

Glycoprotein Integrin beta-3 subunit and Glycoprotein Integrin alpha-2 subunit (GPIIIa/GPIIb)

Glycoproteins IIIa (GPIIIa) and IIb (GPIIb) form the GPIIIa/GPIIb complex that belongs to a class of multisubunit integrin receptors that bind cell adhesion molecules. These receptors are composed of alpha and beta subunits referred to as GPIIb and GPIIIa, respectively. Together the GPIIIa beta and GPIIb alpha subunits form part of the platelet complex receptor, fibronectin receptor, and vitronectin receptor, and play a role in clotting.

The GPIIIa gene encodes a 788 amino acid polypeptide with a 26 residue signal peptide, a 29 residue transmembrane domain near the carboxyterminus and four cysteine rich domains of 33-38 residues each. (Zymrin et al., *J. Clin. Invest.* 81:1470-1475 (1988)). Two different antigenic forms of GPIIIa, alloantigens PlA1 and PlA2 (Platelet Antigen 1 and 2) have been described and can be distinguished using a monoclonal antibody. The most common form of GPIIIa, PlA1, is carried by 98% of the Caucasian population. The rarer form of GPIIIa, PlA2, carries a point mutation or single nucleotide polymorphism at base 192, changing a codon from CTG to CCG thereby causing a leucine to proline substitution at amino acid position 33 (Newman et al., *J. Clin. Invest.* 83:1778-1781 (1989)).

The GPIIb polypeptide is the larger component of the GPIIIa/GPIIb complex and includes two disulfide-linked subunits of 137 amino acids and 871 amino acids respectively. Two antigenic forms of GPIIb, Bak<sup>a</sup> and Bak<sup>b</sup>, have been described and can be distinguished using specific antisera. The rarer form of GPIIb, Bak<sup>b</sup>, has been shown to have a T to G point mutation that results in an isoleucine to serine substitution at amino acid position 843 (Lyman et al., *Blood* 75:2343-2348 (1990)).

The presence of the C-nucleotide at position 192 of GPIIIa DNA can be readily detected by PCR amplification of a region bracketing position 192, followed by MspI digestion of the amplification products, as the C-substitution at that site creates a new MspI restriction site. Alternatively, the sequence at the variance site can be determined using sequencing of the amplification products to identify the nucleotide at the specified position.

The variant GPIIb forms can be detected using similar techniques as for GPIIIa variants by determining the nucleotide at position 2622 (corresponding to amino acid position 843).

It was found that each of the rarer variant sequences described above for GPIIIa and GPIIb correlated with the development of Alzheimer's disease, both separately and together. The variant GPIIIa and GPIIb alleles were found in Alzheimer's patients with an odds ratio of 1.82 and 1.45 respectively as compared to the wild-type alleles. Further, the two variant alleles were found to occur together in Alzheimer's patients as compared to normal subjects with an odds ratio of 3.74.

GPIIIa and GPIIb thus provide examples of variant sequences which result in amino acid substitutions in encoded polypeptides, where the variant sequences are correlated with the development of a disease or condition.

Similarly, other sequence variances in GPIIIa and GPIIb can be analyzed. In GPIIIa, these include for example, arg62term, leu117trp, asp119tyr, ser162leu, arg214gln, arg214trp, cys374tyr, tro407ala, arg636cys, and ser752tro. For GPIIb, the additional variance include leu183tro, gly242asp, the289ser, glu324lys, erg327his, gly418asp, arg553trm, ile565thr, gln747trp, and ser870term. The possible correlation of these variances with the development of cardiovascular disease can also be determined as for the previously identified variances.

### **Example 33**

#### **$\beta$ 2-adrenergic Receptor Polymorphisms and Affects on Outcomes of Congestive Heart Failure**

Several variances have been identified in the gene encoding  $\beta$ -adrenergic receptor. Some of the variances have been shown to affect receptor physiology, and may account, in part, for interpatient variation in the development, progression, and treatment outcomes of congestive heart failure. In a recent study,  $\beta$ -adrenergic receptor polymorphisms were correlated with clinical course of congestive heart failure (CHF) patients. Three amino acid polymorphisms identified in the  $\beta$ -adrenergic receptor were used to stratify patients diagnosed with CHF: Gln27Glu (Glu27 is associated with reduced receptor down-regulation), Arg16Gly (Gly16 is associated with increased down-regulation), and Thr164Ile (Ile 164 is associated with decreased coupling of the receptor with its GTP-binding protein). The allele frequencies of these polymorphisms were similar in normal and CHF patients, suggesting that the polymorphisms are not important in the etiology of CHF.

In a comparison of patients with the 164Ile variance versus the 164Thr variance (more common allele), the investigators determined that survival was greater for the 164Thr variance group over the study period; unadjusted relative risk

was 4.81 as compared to 3.69. The follow-up survival for individuals with the 164Ile genotype was 42% as compared with 76% for the 164Thr individuals. Although at the time of enrollment the two groups had similar clinical symptoms and other characteristics, there appeared to have been speedier decline in the patients with the Ile164 genotype. An analysis of the other two polymorphic sites (positions 16 and 27), revealed no detectable difference. These data taken together suggest that certain polymorphisms in pharmacologically and/or physiologically relevant proteins may influence the course of disease progression, and establishes the importance of determining genotypic differences to be able to identify individuals with specific genotypes in which earlier aggressive therapy would be warranted.

### Example 34

#### Anthracycline Antibiotics

##### *I. Description of Anthracycline Antibiotics*

The anthracyclines are among the most important cancer drugs due to their broad effectiveness against various carcinomas, sarcomas, leukemias and lymphomas. The anthracycline antibiotics, daunorubicin and doxorubicin, were initially isolated from *Streptomyces peucetius* and have been in clinical use for decades. As a result of the effectiveness of these compounds hundreds of analogs have been produced synthetically or isolated from various microorganisms, including the recently developed compound idarubicin. Other recently isolated anthracyclines include DA-125, moflomycin, SM-5887, IT-62-B, WP631, KRN8602, AD198 and MX2 (all of which show antitumor activity), as well as 3'-O-demethyl mutactimycin, 4-O,3'-O-didemethyl mutactimycin and nothramicin (isolated from non-*Streptomyces* species). Many other compounds are known to those skilled in the art. These compounds can intercalate into DNA, and interfere with DNA replication and RNA transcription by steric action and by interfering with topoisomerase II function. The anthracyclines are associated with single- and double-stranded DNA strand scission, as well as production of radicals including superoxide, which induce damage to cellular components, including indirect DNA and protein alkylation. Free radical generation is dependent on cellular cytochrome p450 and quinone or hydroxyquinone moieties on adjacent rings in the anthracene backbone. Anthracyclines also bind membranes and alter membrane fluidity and transport, perhaps by radical formation. The anthracyclines are metabolized via hepatic oxidation to polyalcohols, with subsequent deglycosylation, formation of glucuronides and excretion into both bile and urine.

##### *II. Current Indications for Anthracycline Antibiotics and Derivatives*

Anthracycline antibiotics and derivatives are currently used to treat a broad spectrum of neoplastic diseases including, leukemias, lymphomas, sarcomas, neuroblastomas and cancers of the breast, thyroid, lung, stomach, and urogenital tract (endometrium, ovary, testicle). The synthetic, less cardiotoxic anthracycline derivative, mitoxantrone is indicated for acute nonlymphocytic leukemia (ANLL), and is also active against non-Hodgkins lymphomas and breast cancer.

### III. *Limitations of Current Therapies Utilizing Anthracycline Derivative Antibiotics*

The clinical use of anthracycline derivatives is circumscribed by dose-limiting neutropenia and mucositis, and by cardiac toxicity, including an acute syndrome characterized by conduction and rhythm abnormalities or pump failure, and a chronic syndrome of cardiomyopathy that can lead to congestive heart failure. Anthracyclines are administered intravenously on various schedules. In the past dosing was by iv bolus every 3 or 4 weeks, but it has come to be appreciated that repeated small doses or continuous iv infusion is safer, especially in terms of cardiac toxicity, with no evident loss of efficacy. A major limitation of this family of compounds is that a cumulative dose in excess of 550 mg/square meter puts patients at risk of cardiomyopathy and resulting congestive heart failure. In the range of 1 to 10% of patients receiving a cumulative dose of at least 550 mg/square meter develop cardiomyopathy. Cardiomyopathy develops in a smaller fraction of patients receiving lower cumulative doses. All clinically tested anthracyclines are effective against some lymphomas and leukemias. Doxorubicin is also effective against certain solid tumors, such as those of the breast and lung, and a wide range of sarcomas. Doxorubicin is the drug of choice for the treatment of metastatic thyroid tumors. It is known to produce severe local toxicity to previously irradiated tissues, even when the two therapies are not administered contemporaneously. Although mitoxantrone treatment produces less nausea, vomiting, and alopecia than doxorubicin, acute myelosuppression and mucositis are frequently observed.

### IV. *Impact of Genotyping on Drug Development for Anthracyclines*

The effectiveness of the anthracycline class of chemotherapeutics is believed to be related to its ability to cause DNA damage, either by direct free-radical damage or through the disruption of topoisomerase II function. Other effects of free radicals, which attack a wide range of important biological targets, are also likely to be important. Resistance to treatment can occur through several mechanisms, some of which are well studied. For example, (1) decreased levels of Topoisomerase II are frequently observed in anthracycline resistant cells. Levels of Topoisomerase II

(including TOP2 alpha and TOP2 beta genes) could be influenced by sequence variation or (in cancer tissue) by loss of heterozygosity, affecting interpatient variation in response or toxicity. (2) Topoisomerase III and Topoisomerase III beta levels or function may modulate response to anthracyclines. Anthracycline resistance in experimental systems is often mediated by drug efflux proteins, including the multidrug resistance transporter MDR1 and the multidrug resistance associated protein 1, as well as possibly other members of the ATP-binding cassette family (MRPs 1 through 6). (3) Variation in levels or function of phase I oxidative metabolism, glutathione-S-transferase and peroxidase, lung resistance related protein (LRP), breast cancer resistance protein (BCRP), and topoisomerase II. As anthracycline action is exerted through DNA damage, enzymes involved in the detection and repair of DNA damage (such as members of the xeroderma pigmentosum complementation groups (XP), the excision repair cross-complementation groups (ERCC), p53, the ataxia telangiectasia pathway) could also affect efficacy and toxicity. Polymorphisms in any of these gene pathways that affect the enzymatic activity of a gene product, the amount of a gene product, or the interaction of a gene product with anthracycline derivatives would be expected to affect either the initial response to treatment or systemic toxicity.

There is also evidence that anthracyclines are probably less effective in MSI tumors; resistance attributable to impaired ability to detect DNA damage and thence activate apoptosis, and to increased mutation rate.

Impairment of essential free fatty acid metabolism is believed to play a role in therapeutic effect, as well as cardiac toxicity since administration of L-carnitine has been shown to partially reverse cardiac toxicity. The levels of iron, which serves as a mediator of free-radical damage, are also an important factor in cardiac toxicity, since treatment with the iron chelator, ADR-529 is protective. The levels of enzymes controlling oxidative stress, such as superoxide dismutase, are also known to be important determinants of anthracycline toxicity. Doxorubicin and its metabolite doxorubicinol are known to inhibit the action of ion pumps known to be involved in cardiac muscle contraction such as the sarcoplasmic reticulum calcium-dependent ATPase, SERCA1.

Polymorphisms gene products involved in fatty acid metabolism, iron metabolism, calcium concentration, and free radical quenching that alter total enzymatic activity would all be expected to be predictive of toxicity, particularly if the polymorphism is in a gene product whose expression is restricted to or enriched in cardiac tissue (i.e. SERCA1). As an extension, any polymorphism correlated with reduced cardiac function, either manifest or occult, might predispose patients receiving anthracycline antibiotics or derivatives to cardiac toxicity.

### Example 35

#### Antimicrotubule Agents

##### *I. Description of Vinca and Taxus Alkaloids and Derivatives*

5           The vinca alkaloids, originally extracted from the periwinkle, *Vinca rosea*, and the taxus alkaloid, taxol, isolated from the Western yew, *Taxus brevifolia*, exert their pharmaceutical effects by promoting the destabilization or polymerization, respectively, of microtubule structures involved in cell architecture and division. The vinca alkaloids, and vinorelbine, a newer, better tolerated derivative, share a  
10       heterodimeric, heterocyclic structure and bind tubulin with a 1:1 stoichiometry. Binding prevents mitotic spindle function and normal chromosome segregation, leading to apoptotic cell death. Colchicine, an alkaloid extracted from the autumn crocus, *Colchicum autumnale*, shares this mechanism of action, but its use is restricted to the treatment of gout.. Taxol, and its more potent derivative, docetaxel,  
15       are complex terpenoid compounds that contains a taxane ring nucleus. Treatment with taxus alkaloids causes the accumulation of microtubule aggregates, leading to abnormal cell morphology and arrest of cell division during mitosis. Prior treatment with doxorubicin, which antagonizes cell cycle progression, can reduce therapeutic benefit and increase toxicity. Discodermolide, a polyhydroxylated alkatetraene  
20       lactone, binds tubulin at the same location as taxol, causing tubule aggregation in an analogous manner. Epothilone A and B, isolated from the myxobacterium *Sorangium cellulosum*, and desoxyepothilone B, a less toxic derivative, are also known to exert their antiproliferative effects through microtubule stabilization. Rhizoxin, combretastatin A4, and amphethinile are other recently identified natural  
25       product microtubule inhibitors.

##### *II. Current Indications for Antimicrotubule Agents*

          The vinca alkaloids differ significantly in their antitumor effects as well as actions on normal tissues. Vincristine is a standard component of regimens for  
30       treating pediatric leukemias and solid tumors and is frequently used to treat adult lymphomas. Vinblastine is utilized primarily for the treatment of lymphomas, neuroblastoma, breast and choriocarcinomas, and as a second-line therapy for various solid tumors. The most important use of vinblastine is conjunction with bleomycin and cisplatin in the curative therapy of testicular cancer. Vinorelbine  
35       has been successfully used as a monotherapy to treat non-small cell lung cancer and breast cancer. Treatment is via weekly intravenous infusion until dose-limiting toxicity is observed or triweekly during vinblastine treatment of testicular cancer.

### III. *Limitations of Current Therapies Utilizing Antimicrotubule Agents*

Vinblastine and vinorelbine cause leukopenia and vincristine can cause hypertension through inappropriate vasopressin secretion. Alopecia occurs in approximately 20% of patients receiving vincristine, but is reversible, often without  
5 cessation of treatment. All three vinca alkaloids can cause neurotoxicity, but vincristine has predictable cumulative effects. Neurotoxic symptoms include numbness and tingling of the extremities, loss of deep tendon reflexes, and muscle weakness, the latter prompting suspension or reduction of dosing.

Neutropenia and mucositis are frequently observed during taxol treatment, with peripheral stocking-glove sensory neuropathy seen as the dose-limiting  
10 toxicity. Many patients experience myalgia for several days after dosing. Dosing can be via short (1-6 hour) or long (72-96 hour) infusions. Pretreatment with corticosteroids or antihistamines has been used to avert hypersensitivity reactions seen with shorter dosing schedules and mucositis is a frequent complication of  
15 longer schedules.

Paclitaxel and docetaxel undergo oxidative hepatic metabolism via CYP2C8 and 3A4 and are particularly toxic in patients with reduced liver function.

### IV. *Impact of Genotyping on Drug Development for Antimicrotubule Agents*

The effectiveness of antitubule agents is related to their ability to prevent mitosis by affecting spindle assembly and disassembly, by preventing secretory vesicle translocation, and by perturbing normal cellular architecture. Resistance to treatment can occur through alterations in microtubule-associated protein 4 (MAP4),  
20 beta tubulin (TUBB), multidrug resistance transporter (MDR1), Bcl-X/Bcl-2 binding protein (BAD), and tyrosine kinase type receptor HER2/NEU. Polymorphisms in  
25 any of these gene pathways that affect the enzymatic activity of gene product, amount of gene product, or interaction between gene product and antimicrotubule agent would be expected to affect initial response to treatment.

Since the vinca and taxol classes of antimicrotubule agents have opposing  
30 effects on microtubule polymerization state, resistance to one class of agents is often associated with collateral sensitization to the other. Analogously, tubulin or MAP4 polymorphisms that stabilize microtubules would be expected to respond better to taxol therapy than to vinca alkaloid therapy. Microtubules are composed of alpha and beta tubulin subunits and each is encoded by a 15-20 member, dispersed,  
35 pseudogene-containing, multigene family restricted in expression to a subset of tissues. For instance, alpha-1 and beta-2 tubulins are restricted to the testis. Polymorphisms in these subunits would be expected to affect primarily the efficacy of antimicrotubule agents for the treatment of testicular cancers.



Taxol derivatives are metabolized primarily by cytochrome P450s CYP2C8 and 3A4. Polymorphisms that affect the enzymatic activity or amount of these gene products would be expected to be predictive of toxicity, especially hepatic and neural. Alpha-3, beta-4, and beta-5 tubulin subunits are restricted to differentiated neural tissues and polymorphisms in these genes affecting protein levels or microtubule agent binding might be predictive of neural toxicity.

### Example 36

#### Topoisomerase Inhibitors

##### I. *Description of Topoisomerase Inhibitors*

Etoposide and teniposide are two semisynthetic glycoside derivatives of podophyllotoxin, a toxic alkaloid from the mayapple, *Podophyllum peltatum*. These compounds have a similar spectrum of antitumor activity and exert their cytotoxic effects by their interaction with cellular topoisomerase II, an enzyme required during DNA replication. The complex between DNA topoisomerase II and etoposide or teniposide is capable of double stranded DNA strand scission, but not strand exchange or ligation. The resulting DNA damage initiates apoptotic cell death. The bulk of administered etoposide is excreted via the kidney unchanged whereas approximately 80% of teniposide is recovered from urine as metabolites. Amsacrine, 4-(9-acridinylamino)-N-(methanesulfonyl)-m-anisidine, is an additional inhibitor of DNA topoisomerase II in clinical trials as part of multiagent induction chemotherapeutic regimen for acute myelogenic leukemias.

Topotecan and irinotecan, derivatives of camptothecin, originally isolated from the bark of *Camptotheca acuminata*, bind DNA topoisomerase I and cause DNA fragmentation and apoptotic cell death in a manner entirely analogous to the podophyllotoxins. Topotecan is also oxidized by liver cytochromes prior to being excreted via the kidneys. Irinotecan is a prodrug and requires activation by a carboxylesterase to its active metabolite, SN-38. Elimination after hepatic oxidation is via biliary excretion.

##### II. *Current Indications for Topoisomerase Inhibitors*

Etoposide and teniposide are active against a broad spectrum of tumor types including testicular, small cell lung, various lymphomas, acute granulocytic leukemia, and Kaposi's sarcoma. When combined with cisplatin and bleomycin for testicular tumors and with cisplatin for small cell lung carcinomas, these compounds become the treatment of choice. Administration can be achieved orally (etoposide), but the preferred route is intravenous, with dosing repeated at 2 to 3 day intervals.

Teniposide is better tolerated in patients with compromised renal function than is etoposide.

Topotecan is used primarily for the treatment of ovarian and small cell lung carcinomas and is administered via daily intravenous infusion for 3 or more days.

5 Irinotecan is indicated for the treatment of colorectal cancer and is administered by slow intravenous infusion once weekly for 4 weeks, followed by a two week recovery period. This dosing cycle is repeated until the desired therapeutic endpoint is reached.

### 10 III. *Limitations of Current Therapies Utilizing Topoisomerase Inhibitors*

The dose-limiting toxicity for etoposide is leukopenia which peaks approximately two weeks after the onset of treatment. Nausea, vomiting, stomatitis, and diarrhea occur in about 15% of patients receiving etoposide intravenously and 55% who receive it orally. Hepatic toxicity, phlebitis, dermatitis, and reversible  
15 alopecia are also observed. Etoposide treatment of childhood acute lymphoblastic leukemia (ALL) has been linked with a secondary myeloid/lymphoid or mixed-lineage leukemia involving a translocation event at 11q23, a region involved in pluripotent stem cell differentiation, that appears 1 to 3 years subsequent to therapy. Teniposide is also used for the treatment of refractory ALL and is associated with  
20 myelosuppression, nausea, and vomiting. Undesired effects of topotecan and irinotecan treatment are similar to those of topoisomerase II inhibitors. Nausea associated with irinotecan is often severe enough to require treatment.

### 25 IV. *Impact of Genotyping on Drug Development for Topoisomerase Inhibitors*

Resistance to topoisomerase I and II inhibitor therapy can be caused by alterations in topoisomerase activity, topoisomerase levels, or in inhibitor accumulation (MDR1). Multiple amino acid polymorphisms have been reported for both topoisomerases (Table 3) that could potentially affect enzyme activity, drug binding, or protein levels. It has also been shown that cell lines lacking functional  
30 Ku86, a protein involved in double-stranded DNA break repair, are hypersensitive to etoposide, suggesting that polymorphisms affecting the levels or activity of this protein in normal tissues or tumor might also be an important determinants of toxicity and efficacy, respectively.

A serious undesired outcome of etoposide treatment of ALL is the  
35 development of therapy-related, secondary nonlymphocytic leukemia. Studies have shown that even though etoposide is a known mutagen, mutation rates are not significantly enhanced during treatment, suggesting that patients that acquire secondary leukemia have a natural predisposition. The appearance of secondary

acute myelomonocytic or promyelocytic leukemia is related to DNA translocations involving the 11q23 region that contains the *Drosophila* trithorax homeobox transcription factor homolog MLL or the 15q22 region that contains the PML gene, whose product contains transcription factor consensus elements. The latter  
5 translocation produces a hybrid protein containing the DNA binding portion of the PML protein fused to the hormone binding portion of the retinoic acid receptor alpha protein. The 11q23 region is known to contain folate-sensitive fragile site FRA11B, suggesting that polymorphisms in genes involved in folate metabolism may play a contributing role to the appearance of secondary leukemia.  
10 Polymorphisms in genes involved in non-pathological DNA rearrangements such as immunoglobulin and T-cell receptor rearrangements (i.e. ataxia telangiectasia, DNA ligase, Ku86, Ku70, etc.), that alter the amount or activity of their gene product, represent candidate genes for association with susceptibility to etoposide treatment-related, secondary leukemia.

### Example 37

#### Platinum Coordination Complexes

##### *I. Description of Platinum Coordination Complexes*

The cytotoxic nature of platinum compounds was first observed in *E. coli* in  
20 1965 and traced to inorganic platinum adducts with ammonium and chloride ions. Of the thousands of platinum derivatives that have been synthesized and tested, cisplatin (cis-diaminodichloroplatinum II) and carboplatin (diaminocyclobutanedicarboxylatoplatinum II), have proven most valuable in the clinic. These platinum complexes seem to enter cells by diffusion and are activated  
25 by hydrolysis to a hydrated, cationic diamino platinum II species believed to react with nucleic acids and proteins. The N7 position of guanine is particularly prone to modification and intrastrand and interstrand DNA cross-links between proximal guanine bases and adenine and guanine bases are formed. These adducts inhibit DNA replication and transcription, leading to apoptotic cell death. The bulk of  
30 compound is excreted unchanged in the urine.

##### *II. Current Indications for Platinum Coordination Complexes*

Cisplatin produces good response in a broad range of cancers including those of the bladder, head and neck, endometrium, and small cell lung carcinoma. It has  
35 been used alone, or in combination with paclitaxel, cyclophosphamide, or doxorubicin for the treatment of ovarian cancers and is curative in combination with bleomycin, etoposide, and vincristine in about 85% of testicular cancers. Platinum compounds are also used as sensitizers for radiation therapy. Administration is via

intravenous infusion subsequent to hydration with saline to minimize renal toxicity. Dosing regimens are 20 mg/m<sup>2</sup> for five consecutive days or 100 mg/m<sup>2</sup> given once every four weeks.

5      *III. Limitations of Current Therapies Utilizing Platinum Coordination Complexes*

Marked nausea and vomiting occur in almost all treated patients, but can be controlled with ondasteron or corticosteroids. Renal electrolyte wasting is a frequent occurrence and may lead to tetany and/or seizures. As a result, it is recommended that plasma magnesium levels in patients receiving platinum  
10      compounds are routinely monitored. The most serious adverse effects of platinum coordination compound therapy are neurological. Tinnitus and hearing loss in the high frequency range become more frequent and severe with repeated doses and tend to be more pronounced in children. Cisplatin induced neuropathies were first recognized in the early 1980s. Early indications are reduced decreased vibratory  
15      sensibility in toes, loss of ankle jerks, and loss of sural nerve response. Peripheral nerves may show axonal degeneration and secondary myelin breakdown. Cisplatin-induced peripheral neuropathy may worsen after discontinuation of treatment, can linger for months to years after cessation of treatment, and can result in death.

20      *IV. Impact of Genotyping on Drug Development for Platinum Coordination Complexes*

Resistance to platinum compound therapy is generally acquired through the selection of mutant forms of the tumor suppressor protein p53. This protein is involved in the detection of DNA damage and DNA damage-related cell-cycle arrest  
25      and apoptosis. Tissue culture studies have shown that these mutants appear to arise spontaneously and become enriched only after platinum treatment. Numerous polymorphisms in the p53 gene have been reported and any that reduce protein amounts or DNA binding activity would be expected to correlate with lower treatment efficacy. As the cytotoxicity of platinum coordination complexes are  
30      directly related to their charge and ability to alkylate DNA, enzymes involved in the detection and repair of DNA damage (such as members of the xeroderma pigmentosum complementation groups (XP), the excision repair cross-complementation groups (ERCC), Ku86/70, etc.) could also affect efficacy and toxicity. Elevated levels of some of these enzymes has been found in platinum-  
35      resistant ovarian tumor samples. Polymorphisms in any of these gene pathways that affect the enzymatic activity of gene product, the amount of gene product, or the interaction of gene product with platinum-induced DNA adducts would be expected to affect either the initial response to treatment or systemic toxicity.

Neural platinum toxicity appears to be mediated by free, inorganic platinum. Platinum accumulation is greatest in dorsal root ganglia and lowest in neural tissues protected by the blood-brain barrier, consistent with primarily peripheral toxicity. Several agents including glutathione, metallothionein, nerve growth factor, neurotrophin 3, glutamate, and S-2-(3-aminopropylamino)-ethylphosphorothioic acid (WR 2721) have shown promise in animal models as neuroprotectants.

Glutathione is synthesized from the amino acids cysteine, glutamate, and glycine by the consecutive action of gamma-glutamylcysteine synthetase and glutathione synthetase, encoded by single-copy genes and expressed ubiquitously. Polymorphisms in the genes required for glutathione synthesis would be expected to affect primarily the efficacy of platinum compounds. In contrast, metallothioneins are encoded by a 10 to 12 member multigene family. Metallothionein 3 expression is restricted to neural tissue and polymorphisms could be associated with neural toxicity. Polymorphisms in these genes influencing protein levels or activity would be expected to be important predictors of neural toxicity.

### Example 38

#### Steroid Hormone Derivatives

##### *I. Description of Steroid Hormone Derivatives and Related Agents*

Steroidal agents include adrenocorticosteroids and analogs, agents such as aminoglutethimide that regulate the levels of adrenocorticotrophic hormone (ACTH), antiestrogens such as tamoxifen, progestins such as hydroxyprogesterone caproate and megestrol acetate, antiandrogens such as flutamide, and gonadotropin releasing hormone (GNRH) and analogs such as goserelin and leuprolide, that decrease secretion of leutenizing hormone (LH) and follicle stimulating hormone (FSH) by the pituitary after long term administration. Depression of FSH and LH levels, in turn, decreases circulating levels of testosterone to castration levels in men and estrogen levels in women to postmenopausal.

Flutamide, tamoxifen, panomifene, and raloxifene are recently developed androgen and estrogen receptor modulators that block the activation of transcription required for the maintenance and function of hormone-responsive tissues. In the absence of androgen- or estrogen-stimulated transcription, proliferation of metastatic prostate and breast cancers is greatly reduced. These agents are usually used in conjunction with cytotoxic chemotherapeutic agents such as alkylating agents, platinum compounds, anthracyclines, topoisomerase inhibitors, and microtubule polymerization/depolymerization modulators. Tamoxifen, cyclosporin A, and

verapamil, have all received great clinical attention due to their ability to reverse MDR1-associated drug resistance.

## II. *Current Indications Steroid Hormone Derivatives and Related Agents*

5           Steroidal agents and agents that indirectly affect steroid levels are used against a rather limited number of neoplastic diseases. Corticosteroids such as dexamethasone and prednisone are used alone or in combination with vincristine and anthracyclines, with or without methotrexate and asparaginase, for the treatment of acute and undifferentiated lymphoblastic leukemia, due to their ability to block  
10 lymphocyte proliferation. Aminoglutathimide treatment of metastatic breast cancer with concomitant hydrocortisone supplementation has been largely supplanted by tamoxifen, which acts directly to limit estrogen receptor signaling. The orally available aromatase inhibitors vorozole, letrozole, exemestane, formestane, and anastrozole are currently in development as second-line therapies for the treatment  
15 of advanced breast cancer.

Tumors stemming from endocrine tissues and steroid-responsive tissues frequently retain steroid hormone responsiveness initially. This is true for tumors of breast, prostate, testicular, ovarian, and endometrial origin, as well as other less frequent cancers.

20           Localized prostate cancer is often curable with surgery and/or radiation therapy, but androgen-deprivation therapy becomes the primary hormonal treatment for metastatic disease. Treatment leads to a reduction in symptoms, but is considered palliative since tumors eventually become insensitive. Reduction in serum androgen can be achieved by bilateral orchiectomy, generally reserved for  
25 older patients, GNRH analog treatment, and flutamide treatment alone or in conjunction with GNRH analogs. Flutamide decreases the original flare of prostate tumor growth as a result of transient LH increase in GNRH analog monotherapy. Leuprolide and goserelin are administered via intramuscular and subcutaneous injection and are released slowly into the bloodstream; both agents are also indicated  
30 for the treatment of breast and endometrial cancers. Flutamide is administered orally, generally three times daily and is currently approved only for use in combination therapy.

Tamoxifen has replaced diethylstilbesterol as the hormonal treatment of choice for estrogen receptor-bearing breast cancers. Both tamoxifen and raloxifene  
35 have found recent application for the prevention of postmenopausal decreases in bone density. Tamoxifen is administered by mouth twice daily and is often used for prolonged periods in the context of adjuvant therapy following the initial treatment

of primary breast cancers. The drug is metabolized by oxidation and formation of glucuronides and excreted into the stool via bile.

III. *Limitations of Current Therapies Utilizing Steroid Hormone Derivatives and Related Agents*

As a class, the hormonal agents are extremely well tolerated. Leuprolide, goserelin and flutamide treatment can produce some of the symptoms of menopause including hot flashes, as well as a loss of libido and impotence, but none of these complications is dose limiting. Doses of tamoxifen 20-times the recommended dose are associated with retinal degeneration, but standard doses produce symptoms similar to menopause, weight gain, and gastrointestinal disturbances, none of which is dose limiting. The aromatase inhibitors produce similar side effects. Prolonged use of tamoxifen, such as during adjunct treatment, chemoprevention, or for prevention of postmenopausal osteoporosis, has been linked to the development of endometrial cancers. Patients receiving the standard dose of tamoxifen for two years are twice as likely to develop endometrial cancer than untreated controls.

IV. *Impact of Genotyping on Drug Development for Steroid Hormone Derivatives*

Antiestrogen therapy in the context of chemotherapy is generally indicated only for estrogen-receptor bearing tumors. Estrogen receptor polymorphisms that affect protein levels, DNA or estrogen binding, or interaction with other transcription factors would be expected to correlate with treatment outcome. More-specifically, decreases in any of these parameters should decrease efficacy. Expression of epidermal growth factor receptor (EGFR) and tyrosine kinase-type cell surface receptor HER2/NEU correlates with poor response to tamoxifen even in estrogen receptor positive tumors, but neither EGFR or HER2/NEU appear to be amplified during the course of treatment. As noted above, HER2/NEU expression also correlates with poor prognosis during treatment with antimicrotubule agents, suggesting that ectopic or enhanced expression of growth factor receptors can overcome the growth inhibition caused by cytotoxic agents.

Steroid hormone derivatives are metabolized via cytochrome P450 and flavin containing monooxygenases and by conjugation to sulfates and glucuronates for elimination. Oxidative metabolism of tamoxifen by liver microsomal fractions has been well characterized and involves the formation of 4-hydroxyl, 4'-hydroxyl, N-oxide, N-desmethyl, 3,4-dihydroxyl, and 3,4-epoxyl derivatives. The latter, reactive epoxide species is formed in large amounts in rats, but not mice or humans, and is thought to account for increased liver carcinogenesis in this species. Formation of the N-oxide is believed to be mediated by a flavin containing monooxygenase

(FMO), while other reactions appear to be carried out by cytochromes, especially CYP3A4 (N-demethylation) and 2D6 (4-hydroxylation). Polymorphisms in genes encoding FMO enzymes 1 and 3-5 (FMO2 is inactive), or CYP3A4 and 2D6, or sulfotransferases, or glycosyltransferases that affect protein amount or activity  
5 would be expected to influence efficacy by increasing or decreasing elimination.

Polymorphisms in the gene(s) encoding the enzyme(s) responsible for 3,4-epoxide formation that affect protein amount or activity would be expected to correlate with the mutagenic effects of tamoxifen, especially with the occurrence of treatment-related endometrial cancers.

10

### **Example 39**

#### **Inhibitors of Signal Transduction**

##### ***I. Description of Signal Transduction Inhibitors***

Signal transduction is the processes whereby external cellular stimuli are  
15 converted into changes in protein expression. The usual chain of events is (1) interaction of a ligand with a cell surface receptor, (2) ligand-induced changes in the three-dimensional structure of the receptor, including dimerization, that are transmitted to the cytoplasmic face of the plasma membrane, (3) transmission of these changes to transcription factors in a complex, multienzyme cascade that  
20 generally involves a change in the phosphorylation state of enzymes in the cascade, modulating their activity or ability to interact with other proteins in the cascade, and (4) modulation of the availability or activity of gene specific transcription factors through changes in phosphorylation status, oligomeric state, cellular localization, synthesis, or degradation.

25 Changes in the signal transduction process play a pivotal role in the etiology of neoplastic transformation and disease. The enzymes involved are usually members of a closely-related, multienzyme family, that display complex temporal regulation during development and are differentially expressed in normal tissues. Recent advances in understanding the molecular biology of these pathways and  
30 technical breakthroughs in both combinatorial chemistry and high-throughput screening have added novel, synthetic agents to the small number of known, naturally occurring signal transduction inhibitors.

Current signal transduction inhibitors affect phosphorylation and dephosphorylation steps associated with receptor and soluble kinases as well as  
35 protein phosphatases. Many subtype selective and nonselective inhibitors of protein kinase C (PKC) were initially isolated from natural sources. These include the protein kinase C inhibitors staurosporin, herbimycin A, lavendustin A, and erbstatin, originally isolated from various *Streptomyces* species; the tyrosine



kinase inhibitors emodin, cytovaricin B, angelmicin B, geldanamycin, and genistein isolated from *Talaromyces*, *Streptomyces*, and *Lupinus* species; the phosphatidylinositol 3-kinase inhibitor wortmannin isolated from *Talaromyces flavus*; and the protein phosphatase inhibitor okadaic acid isolated from the black sponge, *Prorocentrum oncauum*. Erbstatins, which bind the ATP-binding site of PKC, also have activity against topoisomerases I and II. Numerous synthetic derivatives of these compounds that enhance stability and availability, as well as novel compounds, have been produced and assayed in biological systems more recently. These include the protein kinase C inhibitors L86-8275, H7, LY333531 (Eli Lilly), safinol (Sphinx/Eli Lilly) and CGP41251 (Ciba-Geigy); the tyrosine kinase inhibitors SU5416 (Sugen), specific for VEGF receptor-associated tyrosine kinase; ZM 252868, ZD1839 (Zeneca), PD153035 (Parke-Davis), and CGP 52411 (Ciba-Geigy), specific for EGF receptor-associated tyrosine kinase, CEP-701 (KT-5555) and K252a, specific for TRK-type receptor-associated tyrosine kinase, KN-62, specific for  $\text{Ca}^{++}$ /calmodulin-dependent protein kinase II; tyrosine kinase inhibitors of the tyrphostin class, as exemplified by AG1714 (4-nitrobenzylidene malononitrile); the phosphatidylinositol 3 kinase inhibitors of the 3-deoxy-D-myoinositol 1-phosphate/1-phosphonate class; the protein serine/threonine phosphatase inhibitor endothall; and the tyrosine phosphatase inhibitor bis(maltolato)oxovanadium(IV).

Bryostatin, a macrolactone originally isolated from marine sponges, inhibits signal transduction through an as yet unknown mechanism, but likely to involve PKC isozymes.

The growth factor 1 family of transmembrane receptors, including epidermal growth factor receptor (EGFR) and members of the ERB-B family, are overexpressed in a wide variety of solid tumors, particularly squamous cell carcinomas of the head and neck, lung, and cervix. The oncogene CBL, implicated in pre/pro B-cell lymphomas, and its cellular counterpart C-CBL, mediate the recycling/degradation of EGFR members. EGFR members are already important therapeutic targets and C-CBL represents an important future drug target.

Mutations in members of the RAS G protein superfamily are the most common initiators of neoplastic transformation, occurring in approximately 40% of colorectal cancers, 90% of pancreatic cancers, 30% of lung adenocarcinomas, and 25% of acute myeloid leukemias. Inhibitors of RAS farnesylation are currently in clinical trials.

RAS control of cell cycle decisions and of transcription factor phosphorylation by Janus kinase (JUNK) is mediated by at least four distinct signaling pathways including the mitogen-activated protein kinases (MAPKs) and

phosphatidyl inositol 3 kinases (PIK3s). Inhibitors designed to members of these multigene families are in early development, show great promise. Silymarin, a flavonoid antioxidant isolated from milk thistle, is a MAPK modulator and has shown great efficacy in the chemoprevention of skin cancer in a mouse model.

5

## II. *Current Indications for Signal Transduction Inhibitors*

Many of the signal transduction inhibitors listed above show promising antineoplastic activity in tissue culture and animal models, but only a few compound are currently in early clinical development. The staurosporine derivative UCN-01 is being tested for activity in advanced or refractory solid tumors, lymphoproliferative disorders, and lymphoid malignancies and SU5416 is being tested in combination therapy with 5-fluorouracil and leucovorin for metastatic colorectal cancer. Bryostatins are in early clinical trials alone, or in combination with cisplatin and paclitaxel for refractory and advanced malignancies including unresectable stomach, esophagus, anus, prostate, or non-small cell lung cancer. It is anticipated that upon further development, members of this class of agents will be indicated for the treatment of a broad range of neoplastic diseases. The phosphatidylinositol 3 kinase inhibitor, wortmannin, has been shown to be active as a radiosensitizer *in vitro*, suggesting potential utility in the radiation therapy of tumors.

20

## III. *Impact of Genotyping on Drug Development for Signal Transduction Inhibitors*

Activation of the MAPK pathway has been shown to correlate with poor prognosis for prostate cancers as well as resistance to androgen ablation therapy. In both colorectal and breast tumors, expression in malignant tissue was elevated while expression in surrounding tissues was normal. The oncogenic potential of MAPKs has been demonstrated in a mouse model, where a lysine to glutamate mutation appears to cause cellular transformation. These findings all highlight the important role of the MAPK pathway in the initiation and progression neoplastic disease.

25

There is also evidence for the direct involvement of the PKC pathway in neoplastic disease: a point mutation at position 294 of alpha-protein kinase C, leading to an aspartic acid to glycine substitution, has been linked to pituitary tumor invasiveness.

30

Overexpression of EGFR has been strongly associated with the transition from superficial to invasive bladder cancers. Enhanced cellular motility is a prerequisite to invasion and can be inhibited in an *in vitro* model by wortmannin, a specific inhibitor of phosphatidylinositol 3 kinase, implicating this class of enzymes in bladder cancer progression. The structurally related ataxia telangiectasia gene product, when mutated, causes a predisposition to malignancy.

35

Polymorphisms in genes encoding receptors and proteins of the signal transduction pathway as detailed above and in Tables 1-3, or related proteins yet to be discovered, which influence protein amounts, activity, interaction with other proteins or drugs, would be expected to have prognostic value for risk assessment, treatment efficacy, and toxicity.

#### Example 40

##### Inhibitors of Cell Cycle Control

###### a) Description of Cell Cycle Control Inhibitors

The control of cell cycle progression and division is through a complex signaling pathway, such as described above, at the heart of which are the cell division cycle (CDC) proteins, CDC kinases (CDCKs), cyclins, cyclin-dependent kinases (CDKs), and cyclin-dependent kinase inhibitors. All exist as members of multigene families that show temporally regulated and tissue-specific expression. Ubiquitin ligases and the ubiquitinated protein proteolysis pathway are involved in modulating cyclin levels during the cell cycle.

Interest in this class of macromolecules as drug development targets was sparked by the observation that the level of various cyclin-dependent kinases and cyclin-dependent kinase inhibitors differed between normal tissues and a wide variety of tumor types and could be prognostic of treatment outcome. Low to absent levels of the cyclin-dependent kinase inhibitor 1B (p27, KIP1) has been shown to be predictive of unfavorable prognosis in a variety of tumors. Ectopic expression of KIP1 in human brain tumor cells has been shown to reverse some of the changes of neoplastic transformation. In contrast, elevated levels of the cyclin-dependent kinase inhibitor 2A (p16, INK4, MTS1), is associated with progression and unfavorable prognosis in prostate and ovarian cancers. This protein is also the target of frequent somatic mutation.

Several natural and synthetic inhibitors of CDK and CDCK function have been isolated. These include flavopiridol, butyrolactone I, and the purine derivatives aminopurvalanol, olomoucine, and roscovitine.

#### II. *Current Indications for Cell Cycle Control Inhibitors*

The CDK and CDCK inhibitors listed above have demonstrated efficacy in a number of transformed cell types in tissue culture, but only flavopiridol is advanced clinical development for refractory and recurrent colorectal cancer, adenocarcinoma of the prostate, lymphocytic leukemia, and non-Hodkin's and mantle cell

lymphomas, either as a monotherapy or in combination with taxol and cisplatin compounds. It is anticipated that upon further development, members of this class of agents will be indicated for the treatment of a broad range of neoplastic diseases and hyperproliferative disorders such as psoriasis and restenosis.

5

### III. *Impact of Genotyping on Drug Development for Cell Cycle Control Inhibitors*

Expression of cyclin-dependent kinase inhibitor 1A (p21/WAF1) is induced by the tumor suppressor protein p53 in response to DNA damage, thereby playing a direct role in

10

mediating p53-induced G1 arrest. Two polymorphisms in the p21 gene, a serine to arginine change at codon 31 a C to T transition in non-coding sequence, show increased prevalence in prostate adenocarcinoma and squamous cell carcinoma of the head and neck. Similarly, low to absent levels of the cyclin-dependent kinase inhibitor, p27/KIP1 are associated with poor clinical outcome in gastric and

15

colorectal cancers. Cyclin D1 expression levels have also been shown to correlate with progression and prognosis in non-small cell lung cancers, estrogen receptor-positive breast cancers, esophageal cancer, and gastric cancers. However, the correlation can be positive or negative, depending upon cancer type, making it likely that cyclin D1 levels are not the directly responsible for neoplastic transformation in these tumors, and that they are a poor prognostic indicator for tumors in general. However, analysis of patients diagnosed with squamous cell carcinomas showed that G/G homozygotes of the silent G/A polymorphism in exon 4 of cyclin D1 tend to exhibit less differentiated tumors and have shorter remission times than G/A heterozygotes

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25

and A/A homozygotes. These findings carried over to various tumor subtypes, including laryngeal and pharyngeal. Polymorphisms in genes encoding cell cycle checkpoint proteins, and proteins involved in cell cycle progress as detailed above and in Tables 1-3, or related proteins yet to be discovered, which influence protein amounts, activity, interaction with other proteins or drugs, would be expected to have prognostic value for risk assessment, treatment efficacy, and toxicity.

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#### **Example 41**

##### Angiogenesis Inhibitors

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##### i. Description of Angiogenesis Inhibitors

The utility of angiogenesis inhibitors for the treatment of solid tumors was first recognized by Folkman and colleagues in 1980. Angiogenesis, the creation of vasculature, is a process that insures that tissues and organs are adequately supplied

with oxygen and nutrients and that toxic metabolites are efficiently removed. Angiogenesis involves the release of growth factor gradients by inadequately supplied tissue, response to these factors mediated by receptors in surrounding vasculature, and proteases and adhesion molecules involved in tissue remodelling. Angiogenesis and neovascularization, inappropriate or abnormal angiogenesis, can be induced by a number of pathological conditions, usually in the context of hypoxia or inflammation.

As rapidly growing cell masses, solid tumors require a constant, plentiful supply of oxygen and nutrients. In larger tumors, perfusion is often inadequate, causing hypoxia and central necrosis. Various classes of compounds including inhibitors of signal transduction (i.e. LY333531), inhibitors of growth factor receptors (i.e. SU5416), protease inhibitors (i.e. KB-R7785, marimastat), and adhesion inhibitors (castanospermine) have shown activity in various models of angiogenesis and against multiple solid tumor types. Compounds showing promise in model systems or currently in development include the peptides aplidine, vascular endothelial growth inhibitor (VEGI), brain-specific angiogenesis inhibitor (BAI1), K1-5 (kringles 1-5 of plasminogen), U-995 (shark cartilage derived), endostatin, angiostatin, an antibody against vascular endothelial growth factor, and macrophage inflammatory protein 2 (MIP2, GRO2); the steroids and terpenoids squalamine, vitamin D3, and retinoic acid; the antibiotics clarithromycin and combretastatin A4; and the synthetic compounds SU5416 (Sugen), TNP-470, COL-3, IM862, PTK787/ZK222584 (Zeneca), CT-2584, KB-R7785, LY333531 (Eli Lilly), BPHA (Shionogi), carboxyamidotriazole, 5,6-dimethylxanthenone-4-acetic acid, and alpha-difluoromethylornithine, an inhibitor of polyamine synthesis.

## II. *Current Indications for Angiogenesis Inhibitors*

Clinical trials of antiangiogenesis agents are underway for a wide variety of refractory and recurrent solid tumor types including Kaposi's sarcoma, non-Hodgkin's lymphoma, astrocytoma, glioblastoma, oligodendroglioma, ovarian, prostate, and renal tumors.

## III. *Impact of Genotyping on Drug Development for Angiogenesis Inhibitors*

Vascular endothelial growth factor (VEGF) gene expression is increased in k-RAS transformed colorectal cells and VEGF expression is required for efficient tumor formation in nude mice but not for cell immortality. VEGF expression is associated with the progression, invasion and metastasis of colorectal cancer and overexpression of VEGF mRNA in the primary tumour is closely correlated with poor prognosis. High pretreatment serum VEGF is associated with poor response to

treatment and unfavorable survival in patients with small cell lung cancer treated with cisplatin and etoposide combination chemotherapy. These findings suggest the importance of this growth factor in tumor proliferation and implicate polymorphisms in VEGF proteins and VEGF receptor as potentially important determinants of prognosis, treatment efficacy, and toxicity.

The plasminogen-derived antiangiogenic peptide, angiostatin binds vitronectin and induces focal adhesion kinase (FAK1) activity in cell culture. FAK1 normally becomes phosphorylated only in response to cell-cell contact or treatment with peptide hormones including cholecystokinin, bombesin, and vasopressin. This observation suggests that the biological effects of angiostatin may relate to subversion of adhesion plaque formation in endothelial cells. The collagen XVIII-derived antiangiogenic peptide, endostatin binds fibulins 1 and 2 and also induces FAK1 activity.

Macrophage metalloproteinase (HME/MMP12) expression levels in hepatocellular tumors correlate well with angiostatin levels, which in turn were inversely correlated with poor survival. Transforming growth factor-beta 1, a key mediator of tumor angiogenesis, inhibits the generation of angiostatin in a pancreatic carcinoma cell line through modulation of the plasminogen activator/plasminogen activator inhibitor system. Generation of angiostatin may also involve an as yet unidentified, secreted disulfide reductase.

Polymorphisms in genes listed above or in Tables 1-3 and including similar genes not yet discovered that encode vascular growth factors, their receptors, and in enzymes involved in their processing that affect enzyme amounts, activity, or interaction with drug molecules could potentially affect neoplastic disease risk and prognosis as well as antiangiogenic treatment efficacy and toxicity.

## **Example 42**

### **Protease Inhibitors**

#### ***I. Description of Protease Inhibitors***

Extracellular proteases play a crucial role in normal tissue remodeling during embryogenesis, growth, and wound healing by modulating the maturation and degradation of growth factors and extracellular matrix components such as elastin and collagen. Proteases play a role in angiogenesis—the potent inhibitors angiostatin and endostatin are proteolytic fragments of plasminogen and collagen 18A1, respectively. Extracellular proteases are involved in the progression of multiple pathological conditions such as osteoporosis and multiple inflammatory disorders including rheumatoid arthritis, multiple sclerosis, and nephritis.

Tumor metastasis, the migration of cells from the primary tumor to distal sites via the lymph or blood vessels, is mechanistically similar to the migration of lymphocytes from the lymph nodes to sites of inflammation, a process known to rely on the action of zinc requiring matrix metalloproteases (MMPs) and to be regulated by corresponding tissue inhibitors of metalloproteinases (TIMPs). Both matrix metalloproteases and their inhibitors occur in large, dispersed multigene families. Levels of MMP 1 and TIMP 1 correlate with metastatic potential and poor treatment outcome in breast, gastric, and colorectal cancers; levels of MMP 2 and TIMP 2 correlate with metastatic potential and poor treatment outcome in renal, urothelial, bladder, and colorectal cancers. Invasion of smooth muscle cell layers by tumor cells is inhibited by TIMPs and transfection of human breast cancer cells with TIMP4 reduces their growth and metastatic potential, suggesting direct involvement of metalloproteases in metastasis.

Several matrix metalloprotease have shown promising activity in tissue culture and *in vivo* models of metastasis including biphenyl sulfonyl-phenylalanine hydroxamic acid (BPHA), KB-R7785, and R-94138; several inhibitors including marimastat, batimastat, and AG3340 (Agouron) are in various stages of clinical development.

## II. *Current Indications for Protease Inhibitors*

Clinical trials of protease inhibitors in progress target advanced lung cancers including small cell and non-small cell; supratentorial glioblastoma multiforme; gliosarcoma; gastric, pancreatic, and metastatic breast cancers; and combination therapy with mitoxantrone and prednisone for hormone refractory prostate cancer. Batimastat has shown promise for the treatment of malignant pleural effusion.

Because proteinase inhibitors are not cytotoxic, their use in anticancer therapies has been in combination with cytotoxic agents such as anthracycline antibiotics, microtubule inhibitors, topoisomerase inhibitors, etc., where they inhibit tumor growth indirectly through their antiangiogenic effects and tumor metastasis directly by inhibition of enzymes required for tumor dispersion.

As metalloproteases have been implicated in tumor metastasis, protease inhibitors may find widespread application for the prophylactic treatment of primary tumors during standard chemotherapeutic regimens to prevent the migration of (resistant) tumor cells to secondary sites.

## III. *Limitations of Current Therapies Utilizing Protease Inhibitors*

Symptoms reported by patients with various malignancies during trials of marimastat included severe joint and muscle pain which were debilitating in >60%

of patients at doses >50 mg twice daily. These symptoms were reversible on discontinuation of the drug, and their incidence was been decreased by reducing the dose to 10 mg twice daily.

5     IV. *Impact of Genotyping on Drug Development for Protease Inhibitors*

Protease inhibitors have great potential in the treatment of neoplastic disease through their apparent ability to inhibit tumor invasion and dispersion. The protease/protease inhibitor systems that have been implicated in this process include the matrix metalloproteinases (MMPs) and their corresponding tissue inhibitors of metalloproteinase (TIMPs), the cathepsins (CTSs), and plasminogen activator (PLAU), plasminogen activator receptor (PLAUR), and plasminogen activator inhibitor (PAI1). As proteases are also involved in the inhibition of the angiogenesis required for tumor growth by releasing the potent inhibitors of angiogenesis, endostatin and angiostatin from collagen and plasminogen, greater understanding of the protease biology involved in these opposing processes will be required before protease inhibitor therapy can realize its full potential.

Serum levels of PLAU, PAI1, and PLAUR are predictors of progression and prognosis in prostate and gastric cancers: higher levels correlate with poor outcome and prophylactic chemotherapy after resection may be warranted for patients displaying high levels. Similarly, the five year relapse rate of patients having node-negative breast cancer with low PAI1 and low cathepsin D (CSTD) was 13% while patients who had greater than the median value for both of these molecules had a 5 year relapse rate of 40%. These data would indicate that at least two different protease systems are active in spread of node negative breast cancer and that measurement of CSTD and PAI1 levels may aid in the decisions to be made when offering adjuvant treatment to these patients. Cathepsin B (CTSB) is overexpressed in tumors of the lung, prostate, colon, breast, and stomach. Abundant extracellular expression of CTSB protein was found in 29 of 40 (72.5%) of esophageal adenocarcinoma specimens by use of immunohistochemical analysis.

A single nucleotide insertional polymorphism at -1607 in the promoter of matrix metalloproteinase 1 (MMP1), where an additional guanine (G) creates an Ets transcription factor binding site, creates an allele that displays significantly higher transcription in normal fibroblasts and in melanoma cells. This polymorphism occurs in the normal population with a frequency of 30%. In contrast, in eight tumor cell lines, this frequency increased to 62.5% ( $P < 0.0001$ ), perhaps because increased levels of MMP1 allow more aggressive matrix degradation, thereby facilitating cancer progression.



Polymorphisms in genes listed above or in Tables 1-3 and including similar genes not yet discovered that encode proteases, their substrates (including adhesion proteins), their inhibitors, and in enzymes involved in their processing that affect enzyme amounts, activity, or interaction with drug molecules could potentially affect neoplastic disease risk and prognosis as well as protease inhibitor treatment efficacy and toxicity.

### Example 43

#### Use of Genotype Information for the Identification of Candidates for Prophylactic Therapy

##### i) Occult Disease Detection and Prophylaxis

The early detection and treatment of neoplastic disease greatly improves prognosis—the prognosis for breast cancer chemotherapy is inversely related to lymph node involvement. Genotyping of polymorphisms known to be associated with increased risk for neoplastic disease would warrant careful monitoring or prophylactic treatment. Patients and practitioners must carefully weigh the benefits and associated undesired toxicities of prophylactic treatment against the risk of disease onset and response to conventional therapies.

Great advances in linking genetic polymorphisms to cancer risk have been made in recent years. Most link polymorphisms in genes involved in drug and xenobiotic metabolism (primarily phase I metabolism) to the appearance of various cancers. As environmental risk factors can be controlled, they can be viewed as modulators of genetic polymorphisms involved in innate risk. These include, but are not restricted to, the genes in the table below, which are known to be polymorphic and polymorphisms have been linked to innate or environmentally induced cancer risk in the scientific literature.

| Associated Polymorphic Gene |        |        |         |            |                                                        |
|-----------------------------|--------|--------|---------|------------|--------------------------------------------------------|
| Cancer                      | Name   | GID    | OMIM_ID | VGX_Symbol |                                                        |
| Bladder                     | GSTM1  | J03819 | 138352  | GEN-9D     | 8824515                                                |
|                             | NAT2   | D90041 | 243401  | GEN-466    | 10510890                                               |
|                             | CYP2D6 | X08007 | 124031  | GEN-1FE    | 8824515                                                |
| Breast                      | CYP17  | M14564 | 202110  | GEN-2Z     | 99415566<br>10519398<br>10404084<br>9950238<br>9067272 |

|            |        |        |        |          |                      |
|------------|--------|--------|--------|----------|----------------------|
|            | CYP1A1 | K03191 | 108330 | GEN-9E   | 10468307<br>10519398 |
|            | COMT   | M58525 | 116790 | GEN-3S   | 10519398             |
|            | NAT2   | D90040 | 243400 | GEN-465  | 10389748             |
|            | HRAS   | J00277 | 190020 | GEN-MH8  | 8385520              |
|            | VDR    | J03258 | 601769 | GEN-2J   | 10344739<br>9613456  |
| Colorectal | MTR    | U73338 | 156570 | GEN-69   | 10498402             |
|            | NAT1   | D90042 | 108346 | GEN-465  | 7627961              |
|            | APC    | M74088 | 175100 | GEN-3MW  | 9973276<br>9869603   |
|            | GSTM1  | J03818 | 138351 | GEN-9D   | 10445390             |
|            | HRAS   | J00279 | 190022 | GEN-MH10 | 2887194              |
|            | MTHFR  | U09806 | 236250 | GEN-4FZ  | 9067278<br>8895734   |

| Associated Polymorphic Gene |        |        |         |            |                     |
|-----------------------------|--------|--------|---------|------------|---------------------|
| Cancer                      | Name   | GID    | OMIM_ID | VGX_Symbol |                     |
| Gastric                     | NAT1   | D90043 | 108347  | GEN-466    | 10585581            |
|                             | MYCL1  | M19720 | 164850  | GEN-MK0    | 9635822             |
|                             | MUC6   | U97698 | 158374  | GEN-LTG    | 9419405             |
|                             | MUC1   | X52228 | 158340  | GEN-33N    | 9076520             |
| Glioma                      | RB1    | M33647 | 180200  | GEN-2K1    | 9210953             |
| Lung                        | CYP1A1 | K03191 | 108330  | GEN-9E     | 9610791<br>10506106 |
|                             | DIA4   | J03934 | 125860  | GEN-12L    | 10397241<br>8528266 |
|                             | MPO    | X04876 | 254600  | GEN-PS     | 9371491             |
|                             | GSTM1  | J03817 | 138350  | GEN-9D     | 10506106<br>7728947 |
|                             | MYCL1  | M19721 | 164851  | GEN-MK1    | 1345822             |
|                             | GSTM3  | J05459 | 138390  | GEN-17O    | 7728947             |
|                             | OGG1   | Y13277 | 601982  | GEN-9O     | 9935223             |
| Melanoma                    | HRAS   | J00278 | 190021  | GEN-MH9    | 2572539             |
| Myeloid Leukemia            | IFNB   | V00546 | 147640  | GEN-TV     | 7912973             |
| Oral                        | GSTP1  | X06547 | 134660  | GEN-19N    | 10376763            |
|                             | CYP2D6 | X08006 | 124030  | GEN-1FE    | 9825835             |
| Ovarian                     | EPHX   | L25878 | 132810  | GEN-29Z    | 8944076             |
| Prostate                    | CYP17  | M14564 | 202110  | GEN-2Z     | 10469617            |
|                             | NAT1   | D90041 | 108345  | GEN-464    | 10211944            |
|                             | VDR    | J03259 | 601770  | GEN-2J     | 8797574             |
| Testicular                  | WT1    | X51630 | 194070  | GEN-32A    | 8056449             |

Table: Polymorphic Genes Linked to Cancer Risk. Column 1, labelled "Cancer" shows commonly observed neoplastic diseases classified by organ or cell-type. Genes for which polymorphisms are linked to cancers listed in column 1 are under the broad heading "Associated Polymorphic Gene." These genes are identified by systematic name, "Name;" Genebank identifier, "GID;" Online Mendelian Inheritance in Man identifier, "OMIM\_ID;" and internal, Variagenics, Inc. identifier, "VGX\_Symbol." In addition, the PubMed database identifier, "PMID," allowing identification of pertinent literature is also given. Worldwide web addresses for the databases mentioned are in the "DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS" section under the subheading "Online Databases."

It is likely that the interplay of multiple polymorphic and non-polymorphic genes is involved in the process of neoplastic transformation with both positive and negative risk associations. But, a patient having several predisposing factors for a given cancer type listed in column 1 of the table above will be at greater risk than a patient having fewer. For example, patients with polymorphisms in glutathione-S-transferase (GST) M3 that reduce expressed levels are more likely to develop lung cancer if they also express low levels of GST M1. One skilled in the art will recognize that knowledge of risk ratios associated with various gene polymorphisms and neoplastic diseases will allow medical practitioners to determine whether prophylactic treatment, including change of habits or environment, preventative chemotherapy, careful monitoring for signs of disease, and prophylactic surgery, are warranted and advisable. Multiple risk-associated allelic loci can be genotyped to direct a course of prophylactic treatment in much the same manner as a high cholesterol count in a blood test carries an increased risk of heart disease and may warrant treatment with a statin-type drug (HMGCoA inhibitor).

It will also be recognized by one skilled in the art that factors including age, sex (in the case of non-gender specific cancers), ethnic background, and environment (including diet, smoking, alcohol consumption, and diet) impact risk determinations and great care must be exercised in extrapolating from one population to another.

## II. *Post-Treatment Prophylaxis*

Notes: Aim is to forestall onset of new disease after successful initial therapy--correlation of tumor genotype with metastatic potential.

KIP1 polymorphisms, WAF1 polymorphisms, EGFR polymorphisms, ERBB2 polymorphisms

5

### Other Embodiments

The invention described herein provides a method for identifying patients with a risk of developing neurological disease or dysfunction by determining the patients allele status for a gene listed in Tables 1-6, 11-17, and 18-23 and providing a forecast of the patients ability to respond to or tolerate a given drug treatment. In particular, the invention provides a method for determining, based on the presence or absence of a polymorphism, a patient's likely response to drug therapies of neurological disease or dysfunction. Given the predictive value of the described polymorphisms a candidate polymorphism is likely to have a similar predictive value for other drugs acting through other pharmacological mechanisms. Thus, the methods of the invention may be used to determine a patient's response to other drugs including, without limitation, antihypertensives, anti-obesity, anti-hyperlipidemic, or anti-proliferative, antioxidants, or enhancers of terminal differentiation.

In addition, while determining the presence or absence of the candidate allele is a clear predictor determining the efficacy of a drug on a given patient, other allelic variants of reduced catalytic activity are envisioned as predicting drug efficacy using the methods described herein. In particular, the methods of the invention may be used to treat patients with any of the possible variances, e.g., as described in Table 3 of Stanton et al., U.S. Application No. 09/300,747.

In addition, while the methods described herein are preferably used for the treatment of human patients, non-human animals (e.g., dogs, cats, sheep, cattle and other bovines, swine, and apes and other non-human primates) may also be treated using the methods of the invention.

It will be readily apparent to one skilled in the art that varying substitutions and modifications may be made to the invention disclosed herein without departing from the scope and spirit of the invention. For example, using other compounds, and/or methods of administration are all within the scope of the present invention. Thus, such additional embodiments are within the scope of the present invention and the following claims.

The invention illustratively described herein suitably may be practiced in the absence of any element or elements, limitation or limitations which is not specifically disclosed herein. Thus, for example, in each instance herein any of the terms "comprising", "consisting essentially of" and "consisting of" may be replaced with either of the other two terms. The terms and expressions which have been employed are used as terms of description and not of limitation, and there is no intention that in the use of such terms and expressions of excluding any equivalents

of the features shown and described or portions thereof, but it is recognized that various modifications are possible within the scope of the invention claimed. Thus, it should be understood that although the present invention has been specifically disclosed by preferred embodiments and optional features, modification and  
5 variation of the concepts herein disclosed may be resorted to by those skilled in the art, and that such modifications and variations are considered to be within the scope of this invention as defined by the appended claims.

In addition, where features or aspects of the invention are described in terms of Markush groups or other grouping of alternatives, those skilled in the art will  
10 recognize that the invention is also thereby described in terms of any individual member or subgroup of members of the Markush group or other group.

Table 1. C. *logy* Gene List

| Class                                                               | Pathway     | Function | Name                                                              | OMIM   | GID           | Locus            |
|---------------------------------------------------------------------|-------------|----------|-------------------------------------------------------------------|--------|---------------|------------------|
| Drug Uptake<br>and Export<br>(additional<br>genes in<br>Toxicology) | Transporter |          | multidrug resistance associated protein<br>MRP1                   | 158343 | L05628        | 16p13.1          |
|                                                                     |             |          | multidrug resistance associated protein<br>MRP2/CMOAT             | 601107 | NM_00039<br>2 | 10q24            |
|                                                                     |             |          | ATP-binding cassette, sub-family C<br>(CFTR/MRP), member 3/CMOAT2 | *****  | NM_00378<br>6 | *****            |
|                                                                     |             |          | ATP-binding cassette, sub-family C<br>(CFTR/MRP), member 4/MOATB  | *****  | NM_00584<br>5 | *****            |
|                                                                     |             |          | ATP-binding cassette, sub-family C<br>(CFTR/MRP), member 5/SMRP   | *****  | NM_00568<br>8 | *****            |
|                                                                     |             |          | ATP-binding cassette, sub-family C<br>(CFTR/MRP), member 9/SUR2   | 601439 | NM_00569<br>1 | *****            |
|                                                                     |             |          | multidrug resistance protein MDR1                                 | 171050 | X96395        | 7q21.1           |
|                                                                     |             |          | multidrug resistance protein MDR3/P-<br>glycoprotein 3/PGY3       | 602347 | X06181        | 7q21.1           |
|                                                                     |             |          | Human sorcin/SRI                                                  | 182520 | L12387        | 7q21.1           |
|                                                                     |             |          | Placenta-specific ATP-binding<br>cassette transporter/ABCP        | 603756 | NM_00482<br>7 | 4q22             |
|                                                                     |             |          | anthracycline resistance-related<br>protein/ARA                   | 603234 | NM_00117<br>1 | 16p13.1          |
|                                                                     |             |          | sulfonylurea receptor<br>(hyperinsulinemia)/SUR                   | 600509 | NM_00035<br>2 | 11p15.1          |
|                                                                     |             |          | Solute carrier family 29, member<br>1/SLC29A1/ENT1                | 602193 | NM_00495<br>5 | 6p21.2-<br>p21.1 |
|                                                                     |             |          | Solute carrier family 29, member<br>2/SLC29A2/ENT2                | 602110 | X86681        | 11q13            |
|                                                                     |             |          | Glutathione-S-transferase 6                                       | 138391 | *****         | *****            |

|                                                                           |                    |                                                                                 |        |               |          |
|---------------------------------------------------------------------------|--------------------|---------------------------------------------------------------------------------|--------|---------------|----------|
| <b>Drug<br/>Metabolism<br/>(additional<br/>genes in<br/>Toxicology)</b>   | <b>Glutathione</b> | Glutathione-S-transferase, alpha<br>1/GSTA1                                     | 138359 | L13269        | 6p12.2   |
|                                                                           |                    | Glutathione-S-transferase, alpha<br>2/GSTA2                                     | 138360 | M15872        | 6p12.2   |
|                                                                           |                    | Glutathione-S-transferase, kappa<br>1/GSTK1                                     | 602321 | *****         | *****    |
|                                                                           |                    | Glutathione-S-transferase 1/MGST1<br>(microsomal)                               | 138330 | AH003674      | Chr.12   |
|                                                                           |                    | Glutathione-S-transferase 2/MGST2<br>(microsomal)                               | 601733 | NM_00241<br>3 | 4q28-q31 |
|                                                                           |                    | Glutathione-S-transferase, mu 1-<br>like/GSTM1L                                 | 138270 | *****         | Chr. 3   |
|                                                                           |                    | 1/GSTM1                                                                         | 138350 | J03817        | 1p13.3   |
|                                                                           |                    | Glutathione-S-transferase, mu<br>2/GSTM2 (muscle)                               | 138380 | NM_00084<br>8 | 1p13.3   |
|                                                                           |                    | Glutathione-S-transferase, mu<br>3/GSTM3 (brain)                                | 138390 | NM_00084<br>9 | 1p13.3   |
|                                                                           |                    | Glutathione-S-transferase, mu<br>4/GSTM4                                        | 138333 | NM_00085<br>0 | 1p13.3   |
|                                                                           |                    | Glutathione-S-transferase, mu<br>5/GSTM5 (brain/lung)                           | 138385 | NM_00085<br>1 | 1p13.3   |
|                                                                           |                    | Glutathione-S-transferase, pi/GSTP1                                             | 134660 | NM_00085<br>2 | 11q13    |
|                                                                           |                    | Glutathione-S-transferase, theta<br>1/GSTT1                                     | 600436 | NM_00085<br>3 | 22q11.2  |
|                                                                           |                    | Glutathione-S-transferase, theta<br>2/GSTT2                                     | 600437 | NM_00085<br>4 | 22q11.3  |
|                                                                           |                    | Glutathione-S-transferase, zeta<br>1/maleylacetoacetate<br>isomerase/MAAI/GSTZ1 | 603758 | NM_00151<br>3 | 14q24.3  |
| <b>Drug<br/>Inactivation<br/>(additional<br/>genes in<br/>Toxicology)</b> |                    |                                                                                 |        |               |          |



|                         |                                                   |          |          |            |
|-------------------------|---------------------------------------------------|----------|----------|------------|
|                         | glutathione reductase                             | 138300   | X15722   | 8p21.1     |
|                         | glutathione peroxidase GPx2                       | 138319   | X68314   | 14q24.1:   |
|                         | glutathione peroxidase GPx3                       | 138321   | X58295   | 5q32-q33.1 |
|                         | glutathione peroxidase GPx1                       | 138320   | Y00433   | 3p21.3     |
|                         | glutathione peroxidase GPx4                       | 138322   | X71973   | 19p13.3    |
|                         | glutathione peroxidase GPx5                       | 603435   | AJ005277 | *****      |
| <b>Metallo-thionein</b> | metallothionein 2a                                | NM_00595 | 3        | 16q13      |
|                         | metallothionein 1g                                | 156360   | J03910   | 16q13      |
|                         | metallothionein 1f                                | 156353   | M10943   | 16q13      |
|                         | metallothionein 1e                                | 156352   | M10942   | 16q13      |
|                         | metallothionein 1b                                | 156351   | AH001510 | 16q13      |
|                         | metallothionein 3                                 | 156349   | NM_00595 | 16q13      |
| <b>Proteolysis</b>      | bleomycin hydrolase                               | 139255   | 4        | 16q13      |
| <b>Methylation</b>      | thiopurine methyltransferase                      | 602403   | X92106   | 17q11.2    |
|                         |                                                   | 187680   | U12387   | 6p22.3     |
| <b>Oxidation</b>        | dehydrogenase/ALDH1                               | 100640   | M26761   | 9q21       |
|                         | myeloperoxidase                                   | 254600   | X04876   | 17q23.1    |
| <b>Acetylation</b>      | N-acetyltransferase 1/NAT1                        | 108345   | NM_00066 | 8p23.1-    |
|                         |                                                   |          | 2        | p21.3      |
|                         | N-acetyltransferase 2/NAT2                        | 243400   | NM_00001 | 8p23.1-    |
|                         |                                                   |          | 5        | p21.3      |
|                         | human DNA mismatch repair protein hMLH1/MutL      | 120436   | U07418   | 3p21.3     |
|                         | xeroderma pigmentosum complementation group A/XPA | 278700   | D14533   | 9q22.3     |
|                         | xeroderma pigmentosum complementation group C/XPC | 278720   | NM_00462 |            |
|                         |                                                   |          | 8        | 3p25       |

|                                                                                                  |        |               |                   |
|--------------------------------------------------------------------------------------------------|--------|---------------|-------------------|
| RAD2 ( <i>S. cerevisiae</i> )<br>homolog/RAD2/excision repair<br>complementation group 5/ERCC5   | 133530 | NM_00012<br>3 | 13q33             |
| RAD23 ( <i>S. cerevisiae</i> ) homolog<br>A/RAD23A                                               | 600061 | NM_00505<br>3 | 19p13.2           |
| RAD23 ( <i>S. cerevisiae</i> ) homolog<br>B/RAD23B                                               | 600062 | NM_00287<br>4 | 3p25.1            |
| RAD26 ( <i>S. cerevisiae</i> )<br>homolog/RAD26/excision repair<br>complementation group 6/ERCC6 | 133540 | NM_00012<br>4 | 10q11             |
| RAD50 ( <i>S. cerevisiae</i> )<br>homolog/RAD50                                                  | 604040 | NM_00573<br>2 | 5q31              |
| RAD51 ( <i>S. cerevisiae</i> ) homolog (E<br>coli RecA homolog)/RAD51                            | 179617 | NM_00287<br>5 | 15q15.1           |
| RAD51 ( <i>S. cerevisiae</i> ) homolog<br>B/RAD51L1                                              | 602948 | Y15572        | 14q23.3-<br>q24   |
| RAD51 ( <i>S. cerevisiae</i> ) homolog<br>D/RAD51L2                                              | 602774 | NM_00287<br>6 | 17q               |
| RAD52 ( <i>S. cerevisiae</i> )<br>homolog/RAD52                                                  | 602954 | NM_00287<br>8 | 17q11             |
| RAD51 ( <i>S. cerevisiae</i> ) homolog<br>C/RAD51L4                                              | 600392 | NM_00287<br>9 | 12p13-<br>q12.2   |
| RAD54 ( <i>S. cerevisiae</i> )-like/RAD54L<br>excision repair complementation<br>group 1/ERCC1   | 603615 | NM_00357<br>9 | 1p32              |
| excision repair complementation<br>group 2/ERCC2/XPD                                             | 126380 | NM_00198<br>3 | 19q13.2-<br>q13.3 |
| excision repair complementation<br>group 1/ERCC3/XPB                                             | 126340 | L47234        | 19q13.2-<br>q13.3 |
|                                                                                                  | 133510 | NM_00012<br>2 | 2q21              |

## DNA Repair

|                                  |                                                                                           |        |               |                    |
|----------------------------------|-------------------------------------------------------------------------------------------|--------|---------------|--------------------|
| DNA<br>Replication<br>and Repair | excision repair complementation<br>group 4/ERCC4                                          | 133520 | NM_00523<br>6 | 16p13.3-<br>p13.13 |
|                                  | replication protein A1 (70kD)/RPA1                                                        | 179835 | NM_00294<br>5 | 17p13.3            |
|                                  | replication protein A2 (32kD)/RPA2                                                        | 179836 | NM_00294<br>6 | 1p35               |
|                                  | replication protein A3 (14kD)/RPA3                                                        | 179837 | NM_00294<br>7 | 7p22               |
|                                  | excision repair protein ERCC1                                                             | 126380 | M13194        | 19q13.2-<br>q13.3  |
|                                  | mismatch repair protein hMSH2                                                             | 120435 | U03911        | 2p22-p21           |
|                                  | O6 alkylguanine-DNA<br>alkyltransferase                                                   | 156569 | M60761        | 10q24.33-<br>qter  |
|                                  | ADP-ribosyltransferase (NAD <sup>+</sup> ; poly<br>(ADP-ribose)<br>polymerase)/PARP/ADPRT | 173870 | NM_00161<br>8 | 1q42               |
|                                  | poly (ADP-ribose)<br>glycohydrolase/PARG                                                  | 603501 | NM_00363<br>1 | 10q11.23           |
|                                  | APEX nuclease (multifunctional DNA<br>repair enzyme)/APEX                                 | 107748 | NM_00164<br>1 | 14q12              |
|                                  | 8-oxoguanine DNA<br>glycosylase/OGG1                                                      | 601982 | NM_00254<br>2 | 3p26.2             |
|                                  | N-methylpurine-DNA<br>glycosylase/MPG                                                     | 156565 | NM_00243<br>4 | 16pter-<br>p13.3   |
|                                  | topoisomerase IIb                                                                         | 126431 | U54831        | 3p                 |
|                                  | topoisomerase IIa                                                                         | 126430 | J04088        | 17q21-q22:         |
|                                  | topoisomerase I                                                                           | 126420 | J03250        | 20q12-<br>q13.1    |
| Replication                      |                                                                                           |        |               |                    |

|                                 |                                         |                  |                         |                             |
|---------------------------------|-----------------------------------------|------------------|-------------------------|-----------------------------|
| <b>Mitosis</b>                  | beta tubulin 2/TUBB2                    | 602660           | NM_00608<br>8           | *****                       |
|                                 | beta tubulin 4/TUBB4                    | 602661           | NM_00608<br>6           | *****                       |
|                                 | beta tubulin 5/TUBB5                    | 602662           | NM_00608<br>7           | *****                       |
|                                 | gamma tubulin/TUBG                      | 191135           | NM_00107<br>0           | *****                       |
| <b>Histone<br/>Acetylation</b>  | histone acetyltransferase               |                  |                         |                             |
|                                 | histone deacetylase                     | 603053           | AF030424                | 2q31.2-<br>q33.1            |
|                                 |                                         | 601241           | U50079                  | 1p34.1                      |
| <b>Telomere<br/>Maintenance</b> | telomerase protein component 1          | 601686           | U86136                  | 14q11.2                     |
|                                 | telomerase reverse transcriptase        | 187270           | AF015950                | 5p15.33                     |
|                                 | telomerase RNA component                | 602322           | U86046                  | 3q21-q28                    |
| <b>DNA<br/>Methylation</b>      | DNA methyltransferase DNMT1             | 126375           | X63692                  | 19p13.3-<br>p13.2           |
|                                 | DNA methyltransferase DNMT2             | 602478           | AF012128                | 10p15.1                     |
|                                 | DNA methyltransferase DNMT3A            | 602769           | AF067972                | 2p23                        |
|                                 | DNA methyltransferase DNMT3B            | 602900           | NM_00689<br>2           | 20q11.2                     |
|                                 | thymidylate synthetase                  | 188350           | X02308                  | 18p11.32                    |
|                                 | cytidine deaminase                      | 123920           | L27943                  | 1p36.2-p35                  |
|                                 | DPD                                     | 274270           | U09178                  | 1p22                        |
|                                 | deoxycytidine kinase                    | 125450           | M60527                  | 4q13.3-<br>q21.1            |
|                                 | Soluble thymidine kinase 1/TK1<br>2/TK2 | 188300<br>188250 | NM_00325<br>8<br>U77088 | 17q25.2-<br>q25.3<br>Chr.16 |

|                              |                                                |        |           |               |  |
|------------------------------|------------------------------------------------|--------|-----------|---------------|--|
| <b>Nucleotide Metabolism</b> | <b>Pyrimidines</b>                             |        |           |               |  |
|                              | uridine kinase                                 | 191730 | NM_003364 | Chr.7         |  |
|                              | uridine monophosphate kinase                   | 191710 | NM_005267 | 1p32          |  |
|                              | uridine phosphorylase                          | 191730 | NM_003364 | Chr.7         |  |
|                              | thymidine phosphorylase                        | 131222 | M58602    | 22q13.32-qter |  |
|                              | aspartate transcarbamylase/CAD                 |        |           |               |  |
|                              | trifunctional protein                          | 114010 | NM_004341 | 2p21          |  |
|                              | orotate phosphoribosyl transferase             | 258900 | NM_000373 | 3q13          |  |
|                              | hypoxanthine-guanine phosphoribosyltransferase | 308000 | M31642    | Xq26-q27.2    |  |
|                              | adenosine phosphoribosyltransferase/APRT       | 102600 | NM_000485 | 16q24         |  |
| <b>Purines</b>               | thiopurine S-methyltransferase/TPMT            | 187680 | NM_000367 | 6p22.3        |  |
|                              | urate oxidase                                  | 191540 | AH003594  | 1p22          |  |
|                              | adenylosuccinate synthetase/ADSS               | 103060 | NM_001126 | 1cen-q12      |  |
|                              | adenylosuccinate lyase                         | 103050 | NM_000026 | 22q13.1       |  |
|                              | glycinamide ribotide formyltransferase         | 138440 | X54199    | 21q22.1       |  |
|                              | purine nucleoside phosphorylase                | 164050 | NM_000270 | 14q13.1       |  |
|                              | xanthine oxidase                               | 278300 | NM_000379 | 2p23-p22      |  |
|                              | adenosine deaminase                            | 102700 | NM_000022 | 20q13.11      |  |

| Cellular Metabolism                                                      | Ribo-nucleotides      | ribonucleotide reductase M1 subunit       |  |  |  |  |
|--------------------------------------------------------------------------|-----------------------|-------------------------------------------|--|--|--|--|
|                                                                          |                       | ribonucleotide reductase M2 subunit       |  |  |  |  |
| General                                                                  | General               | ecto-5'-nucleotidase (CD73)/NT5           |  |  |  |  |
|                                                                          |                       | alkaline phosphatase                      |  |  |  |  |
| Amino Acid Metabolism                                                    | Amino Acid Metabolism | asparagine synthetase                     |  |  |  |  |
|                                                                          |                       | arginase (ARG1)                           |  |  |  |  |
| Steroid Metabolism<br>(additional genes in Endocrinology and Metabolism) | Steroid Metabolism    | arginase (ARG2)                           |  |  |  |  |
|                                                                          |                       | ornithine transaminase                    |  |  |  |  |
| Steroid Metabolism                                                       | Steroid Metabolism    | cytochrome P450 aromatase (CYP19)         |  |  |  |  |
|                                                                          |                       | steroid 5 alpha reductase                 |  |  |  |  |
| Steroid Metabolism                                                       | Steroid Metabolism    | estrogen sulfotransferase                 |  |  |  |  |
|                                                                          |                       | steroid 5-alpha reductase 2               |  |  |  |  |
| Steroid Metabolism                                                       | Steroid Metabolism    | HMGCoA reductase                          |  |  |  |  |
|                                                                          |                       | squalene synthetase                       |  |  |  |  |
| Steroid Metabolism                                                       | Steroid Metabolism    | Folate Receptor Alpha/FOLR1               |  |  |  |  |
|                                                                          |                       | Folate Receptor Beta/FOLR2                |  |  |  |  |
| Steroid Metabolism                                                       | Steroid Metabolism    | Folate Receptor Gamma/FOLR3               |  |  |  |  |
|                                                                          |                       | Folate Transporter (SLC19A1)              |  |  |  |  |
| Steroid Metabolism                                                       | Steroid Metabolism    | Vitamin B12 binding protein               |  |  |  |  |
|                                                                          |                       | folylpolyglutamate synthetase/FPGS        |  |  |  |  |
| Steroid Metabolism                                                       | Steroid Metabolism    | gamma-glutamyl hydrolase/GGH              |  |  |  |  |
|                                                                          |                       | Methylenetetrahydrofolate reductase/MTHFR |  |  |  |  |
| Steroid Metabolism                                                       | Steroid Metabolism    | Dihydrofolate reductase/DHFR              |  |  |  |  |

|                      |                      |                                                                                                                                                           |        |           |              |
|----------------------|----------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------|--------|-----------|--------------|
| Folate<br>Metabolism | Folate<br>Metabolism | 5,10-methylenetetrahydrofolate<br>dehydrogenase, 5,10-<br>methylenetetrahydrofolate<br>cyclohydrolase, 10-<br>formyltetrahydrofolate<br>synthetase/MTHFD1 | 172460 | NM_005956 | 14q24        |
|                      |                      | 5,10-methylenetetrahydrofolate<br>synthetase (5-formyltetrahydrofolate<br>cyclo-ligase)/MTHFS                                                             | 604197 | NM_006441 | Chr. 15      |
|                      |                      | phosphoribosylglycinamide<br>formyltransferase,<br>phosphoribosylglycinamide<br>synthetase,                                                               |        |           |              |
|                      |                      | phosphoribosylaminoimidazole<br>folate hydrolase 1/FOH1                                                                                                   | 138440 | NM_000819 | 21q22.1      |
|                      |                      | 6-pyruvoyl tetrahydrobiopterin<br>synthase/PTPS                                                                                                           | 600934 | NP_004467 | 11q14        |
|                      |                      | serine hydroxymethyltransferase 1<br>(soluble)/SHMT1                                                                                                      | 261640 | Q03393    | 1q22.3-q23.2 |
|                      |                      | serine hydroxymethyltransferase 2<br>(mitochondrial)/SHMT2                                                                                                | 182144 | NM_004169 | 17p11.2      |
|                      |                      | Glycine aminotransferase/glycine<br>cleavage T protein/GAT                                                                                                | 138450 | NM_005412 | 12q13        |
|                      |                      | 5-methylenetetrahydrofolate-<br>homocysteine<br>methyltransferase/methionine<br>glutamate                                                                 | 238310 | NM_000481 | 3p21.2-p21.1 |
|                      |                      | formiminotransferase/dihydrofolate<br>synthetase                                                                                                          | 156570 | NM_000254 | 1q43         |
|                      |                      |                                                                                                                                                           | 229100 | *****     | *****        |

|                            |                            |                                                         |        |               |           |
|----------------------------|----------------------------|---------------------------------------------------------|--------|---------------|-----------|
| Protein<br>Modification    | Prenylation                | farnesyl:protein transferase<br>alpha/FNTA              | 134635 | NM_00202<br>7 | 8p22-q11  |
|                            |                            | farnesyl:protein transferase beta/FNTB                  | 134636 | NM_00502<br>3 | 14q23-q24 |
|                            |                            | Rab geranylgeranyltransferase, alpha<br>subunit/RABGGTA | 601905 | NM_00458<br>1 | 14q11.2   |
| Polyamine<br>Metabolism    | Polyamine<br>Metabolism    | Rab geranylgeranyltransferase, beta<br>subunit/RABGGTB  | 179080 | NM_00458<br>2 | 1p31-p22  |
|                            |                            | ornithine decarboxylase 1 (ODC1)                        | 165640 | M16650        | 2p25      |
|                            |                            | SAM decarboxylase                                       | 180980 | M21154        | 6q21-q22  |
| Phospholipid<br>Metabolism | Phospholipid<br>Metabolism | glucosylceramide synthase                               | 602874 | D50840        | 9q31      |
|                            |                            | interferon alpha1 (IFNa1)                               | 147660 | X02956        | 9p22      |
|                            |                            | interferon alpha2 (IFNa2)                               | 147562 | *****         | 9p22      |
|                            |                            | interferon beta1 (IFNb1)                                | 147640 | V00546        | 9p21      |
|                            |                            | interferon beta3 (IFNb3)                                | 147860 | *****         | Chr.8     |
|                            |                            | interferon omega1 (IFNw1)                               | 147553 | X02669        | 9p21      |
|                            |                            | interferon gamma (IFNg)                                 | 147570 | L07633        | 12q14     |
|                            |                            | interleukin 1 alpha (IL1a)                              | 147760 | M15329        | 2q14      |
|                            |                            | interleukin 1 beta (IL1b)                               | 147720 | K02770        | 2q14      |
|                            |                            | interleukin 2 (IL2)                                     | 147680 | X01586        | 4q26-q27  |
|                            |                            | interleukin 3 (IL3)                                     | 147740 | M20137        | 5q31.1    |
|                            |                            | interleukin 4 (IL4)                                     | 147780 | M13982        | 5q31.1    |
|                            |                            | interleukin 5 (IL5)                                     | 147850 | X04688        | 5q31.1    |
|                            |                            | interleukin 6 (IL6)                                     | 147620 | M14584        | 7p21      |
|                            |                            | interleukin 7 (IL7)                                     | 146660 | J04156        | 8q12-q13  |
|                            |                            | interleukin 8 (IL8)                                     | 146930 | M26383        | 4q12-q13  |
|                            |                            | interleukin 9 (IL9)                                     | 146931 | X17543        | 5q31.1    |
|                            |                            | interleukin 10 (IL10)                                   | 124092 | M57627        | 1q31-q32  |



|                                       |        |           |                |
|---------------------------------------|--------|-----------|----------------|
| interleukin 11 (IL11)                 | 147681 | X58377    | 19q13.3-q13.4  |
| interleukin 12a (IL12a)               | 161560 | NM_002187 | 3p12-q13.2     |
| interleukin 12b (IL12b)               | 161561 | NM_000440 | 5q31.1-q33.1   |
| interleukin 13 (IL13)                 | 147683 | X69079    | 5q31           |
| interleukin 15 (IL15)                 | 600554 | U14407    | 4q31           |
| interleukin 16 (IL16)                 | 603035 | NM_004513 | *****          |
| interleukin 18 (IL18)                 | 600953 | *****     | 11q22.2-q22.3  |
| interferon alpha receptor 1 (IFNAR1)  | 107450 | X77722    | 21q22.1        |
| interferon alpha receptor 2 (IFNAR2)  | 147569 | U68755    | 21q22.1-q22.2  |
| (IFNGR1)                              | 107470 | J03143    | 6q23-q24       |
| interferon gamma receptor 2 (IFNGR2)  | 602376 | NM_000874 | 21q22.1        |
| interleukin 1 receptor 1 (IL-1R1)     | 147810 | M27492    | 2q12           |
| interleukin 1 receptor 2 (IL-1R2)     | 147811 | NM_004633 |                |
| interleukin 2 receptor alpha (IL-2Ra) | 147730 | X01057    | 2q12-q22       |
| interleukin 2 receptor beta (IL-2Rb)  | 146710 | M26062    | 10p15-p14      |
| interleukin 2 receptor gamma (IL-2Rg) | 308380 | D11086    | 22q11.2-q13    |
| interleukin 3 alpha receptor (IL-3aR) | 308385 | M74782    | Xq13           |
| interleukin 4 receptor (IL-4R)        | 147781 | X52425    | Xp22.3         |
| interleukin 5 receptor alpha (IL-5Ra) | 147851 | M96652    | 16p12.1-p11.2  |
| interleukin 6 receptor (IL-6R) (20)   | 147880 | X12830    | 3p26-p24; 1q21 |

## Cytokines

|                                                                |        |               |           |
|----------------------------------------------------------------|--------|---------------|-----------|
| interleukin 7 receptor (IL-7R)                                 | 146661 | M29696        | 5p13      |
| interleukin 8 receptor alpha (IL-8Ra)                          | 146929 | M68932        | 2q35      |
| interleukin 8 receptor beta (IL-8Rb)                           | 146928 | M94582        | 2q35      |
| interleukin 9 receptor (IL-9R)                                 | 300007 | M84747        | Xq28      |
| 10Ra)                                                          | 146933 | U00672        | 11q23.3   |
| interleukin receptor 11 alpha (IL-11a)                         | 600939 | U32324        | 9p13      |
| interleukin receptor 12 beta (IL-12b)                          | 600939 | U03187        | 9p13      |
| 12b2)                                                          | 601642 | U03187        | 1p31.2    |
| interleukin receptor 13 alpha (IL-13a)                         | 300119 | S80963        | Chr.X     |
| 13a2)                                                          | 300130 | X95302        | Xq24      |
| 15Ra)                                                          | 601070 | U31628        | 10p15-p14 |
| tumor necrosis factor alpha/TNFA                               | 191160 | X01394        | 6p21.3    |
| tumor necrosis factor<br>beta/TNFB/lymphotoxin alpha/LTA       | 153440 | NM_00059<br>5 | 6p21.3    |
| tumor necrosis factor ligand<br>superfamily, member 4/TNFSF4   | 603594 | NM_00332<br>6 | 1q25      |
| tumor necrosis factor ligand<br>superfamily, member 5/TNFSF5   | 308230 | NM_00007<br>4 | Xq26      |
| tumor necrosis factor ligand<br>superfamily, member 6/TNFSF6   | 134638 | *****         | 1q23      |
| tumor necrosis factor ligand<br>superfamily, member 7/TNFSF7   | 602840 | NM_00125<br>2 | 19p13     |
| tumor necrosis factor ligand<br>superfamily, member 8/TNFSF8   | 603875 | NM_00124<br>4 | 9q33      |
| tumor necrosis factor ligand<br>superfamily, member 10/TNFSF10 | 603598 | NM_00381<br>0 | 3q26      |
| tumor necrosis factor ligand<br>superfamily, member 11/TNFSF11 | 602642 | NM_00370<br>1 | 13q14     |
| tumor necrosis factor ligand<br>superfamily, member 12/TNFSF12 | 602695 | NM_00380<br>9 | 17p13.3   |

**Inflammation**  
(additional  
genes in  
Immunology)

|                                               |                                                               |        |             |              |
|-----------------------------------------------|---------------------------------------------------------------|--------|-------------|--------------|
| Inflammation (additional genes in Immunology) | tumor necrosis factor ligand superfamily, member 13B/TNFSF13B | 603969 | NM_006573   | 13q32-q34    |
|                                               | tumor necrosis factor ligand superfamily, member 15/TNFSF15   | 604052 | *****       | 9q33         |
|                                               | macrophage inflammatory protein 1 alpha                       | 182283 | M23178      | 17q11-q21    |
|                                               | tumor necrosis factor ligand superfamily, member 18/TNFSF18   | 603898 | *****       | 1q23         |
|                                               | myeloid progenitor inhibitory factor 1                        | 602494 | *****       | *****        |
|                                               | macrophage inflammatory protein 1 alpha                       | 182283 | M23178      | 17q11-q21    |
|                                               | 2',5'-oligoadenylate synthetase 1 (OAS1)                      | 164350 | NM_006187   | 12q24.2      |
|                                               | 2',5'-oligoadenylate synthetase 2 (OAS2)                      | 603350 | M87284      | 12q24.2      |
|                                               | 2',5'-oligoadenylate synthetase 3 (OAS3)                      | 603351 | *****       | 12q24.2      |
|                                               | arachidonate 5' lipoxygenase/ALOX5                            | 152390 | J03571      | Chr.10       |
| Interferon Response                           | arachidonate 12-lipoxygenase/ALOX12                           | 152391 | NM_000697   | 17p13.1      |
|                                               | prostaglandin endoperoxide synthetase 1/COX1/PTGS1            | 176805 | AH001520    | 9q32-q33.3   |
|                                               | prostaglandin endoperoxide synthetase 2/COX2/PTGS2            | 600262 | NM_000963   | 1q25.2-q25.3 |
|                                               | thromboxane A synthase 1/TBXAS1                               | 274180 | SEG_D34613S | 7q34         |
|                                               | prostaglandin D2 synthase                                     | 602598 | M61900      | *****        |
|                                               | prostaglandin I2 synthase/prostacyclin synthase/PTGIS         | 601699 | SEG_D83393S | 20q13        |
|                                               |                                                               |        |             |              |
|                                               |                                                               |        |             |              |
|                                               |                                                               |        |             |              |
|                                               |                                                               |        |             |              |

|               |                                                       |        |            |              |
|---------------|-------------------------------------------------------|--------|------------|--------------|
| Prostaglandin | prostaglandin E receptor 1, EP1 subtype/PTGER1        | 176802 | NM_000955  | 19p13.1      |
|               | prostaglandin E receptor 2, EP2 subtype/PTGER2        | 176804 | *****      | 5p13.1       |
| n             | prostaglandin E receptor 3, EP3 subtype/PTGER3        | 176806 | NM_000957  | 1p31.2       |
|               | prostaglandin E receptor 4, EP4 subtype/PTGER4        | 601586 | NM_000958  | 5p13.1       |
|               | prostaglandin F receptor/PTGFR                        | 600563 | L24470     | 1p31.1       |
|               | prostaglandin F2 receptor negative regulator/PTGFRN   | 601204 | U26664     | 1p13.1-q21.3 |
|               | prostaglandin I2 receptor/PTGIR/prostacyclin receptor | 600022 | SEG_HUM IP | 19q13.3      |
|               | 15-hydroxyprostaglandin dehydrogenase/HPGD            | 601688 | NM_000860  | 4q34-q35     |
|               | aldo-keto reductase family 1, member C2/AKR1C2        | 600450 | NM_001353  | 10p15-p14    |
|               | integrin alpha 1                                      | 192968 | Y00796     | Chr.5        |
|               | integrin alpha 2                                      | 192974 | X17033     | 5q23-q31     |
|               | integrin alpha 4                                      | 192975 | L12002     | 2q31-q32     |
|               | integrin alpha 5                                      | 135620 | NM_002205  | 12q11-q13    |
|               | integrin alpha 6                                      | 147556 | X59512     | Chr.2        |
|               | integrin alpha 7                                      | 600536 | AF032108   | 12q13        |
|               | integrin alpha 8                                      | 604063 | L36531     | *****        |
|               | integrin alpha 9                                      | 603963 | L24158     | *****        |
|               | integrin alpha 10                                     | 604042 | AF074015   | *****        |
|               | integrin alpha D                                      | 602453 | U40279     | 16p11.2      |
|               | integrin alpha M                                      | 120980 | J04145     | 16p11.2      |

|                 |                  |                                                                                  |        |          |            |
|-----------------|------------------|----------------------------------------------------------------------------------|--------|----------|------------|
| <b>Adhesion</b> | <b>Integrins</b> | integrin alpha X                                                                 | 151510 | M81695   | 16p11.2    |
|                 |                  | integrin beta 1                                                                  | 135630 | U28252   | 10p11.2    |
|                 |                  | integrin beta 2                                                                  | 600065 | M15395   | 21q22.3    |
|                 |                  | integrin beta 3                                                                  | 173470 | M35999   | 17q21.32   |
|                 |                  | integrin beta 4                                                                  | 147557 | X51841   | 17q11-qter |
|                 |                  | integrin beta 5                                                                  | 147561 | M35011   | *****      |
|                 |                  | integrin beta 6                                                                  | 147558 | M35198   | Chr.2      |
|                 |                  | integrin beta 7                                                                  | 147559 | M68892   | 12q13.13   |
|                 |                  | integrin beta 8                                                                  |        | NM_00221 |            |
|                 |                  |                                                                                  | 604160 | 4        | *****      |
|                 |                  | cadherin 2/NCAD/CDH2                                                             | 114020 | Z27440   | 18q11.2    |
|                 |                  | human cell adhesion protein SQM1                                                 | 603842 | NM_00414 | 19p13.12-  |
|                 |                  |                                                                                  |        | 6        | p13.11     |
|                 | <b>Proteases</b> | matrix metalloproteinase 3,<br>stromelysin 1                                     |        | NM_00242 |            |
|                 |                  |                                                                                  | 185250 | 2        | 11q23      |
|                 |                  | matrix metalloproteinase 1,<br>aminopeptidase A/glutamyl<br>aminopeptidase/ENPEP | 120353 | M13509   | 11q22-q23  |
|                 |                  |                                                                                  | 138297 | L14721   | 4q25       |
|                 |                  | mammary serine protease/protease<br>M/neurosin                                   | 602652 | D78203   | 19q13.3    |
|                 |                  | protease inhibitor 5/maspin                                                      |        | NM_00263 |            |
|                 |                  | activator                                                                        | 154790 | 9        | 18q21.3    |
|                 |                  | cathepsin B                                                                      | 191840 | AH007073 | 10q24      |
|                 |                  |                                                                                  | 116810 | M14221   | 8p22       |
|                 |                  | type 2 plasminogen activator inhibitor                                           |        | NM_00257 |            |
|                 |                  | urokinase-type plasminogen activator<br>receptor                                 | 173390 | 5        | 18q21.3    |
|                 |                  |                                                                                  | 173391 | NM_00265 |            |
|                 |                  |                                                                                  |        | 9        | 19q13      |

|                                                                             |        |               |                   |
|-----------------------------------------------------------------------------|--------|---------------|-------------------|
| RAD1 (S. pombe) homolog/RAD1                                                | 603153 | NM_00285<br>3 | 5p13.3-<br>p13.2  |
| RAD9 (S. pombe) homolog/RAD9                                                | 603761 | NM_00458<br>4 | 11q13.1-<br>q13.2 |
| RAD17 (S. pombe) homolog/RAD17                                              | 603139 | NM_00287<br>3 | 4q13.3-<br>q21.2  |
| FRAP-related protein/FRP1/ATR                                               | 601215 | U49844        | 3q22-q24          |
| HUS1 (S. pombe) checkpoint<br>homolog/HUS1                                  | 603760 | NM_00450<br>7 | 7p13-p12          |
| ataxia telangiectasia mutated<br>(complementation groups A, C and<br>D)/ATM | 208900 | NM_00005<br>1 | 11q22.3           |
| CHK1 (checkpoint, S.pombe)<br>homolog/CHEK1                                 | 603078 | NM_00127<br>4 | 11q22-q23         |
| growth arrest and DNA-damage-<br>inducible, alpha/GADD45A                   | 126335 | NM_00192<br>4 | 1p34-p12          |
| BRCA1                                                                       | 113705 | NM_00005<br>8 | 17q21             |
| BRCA2                                                                       | 600185 | NM_00005<br>9 | 13q12.3           |
| benzimidazoles 1 (yeast<br>homolog)/BUB1                                    | 602452 | AF139363      | 2q12-q14          |
| benzimidazoles 1 (yeast homolog),<br>beta/BUB1B                             | 602860 | NM_00121<br>1 | 15q14-q21         |
| benzimidazoles 1 (yeast<br>homolog)/BUB3                                    | 603719 | NM_00472<br>5 | 10q24-q26         |
| MAD (mothers against<br>decapentaplegic) homolog 1/MADH1                    | 601595 | NM_00590<br>0 | 4q28              |
| MAD (mothers against<br>decapentaplegic) homolog 2/MADH2                    | 601366 | NM_00590<br>1 | 18q21             |

**DNA  
Damage  
Checkpoint**

|                                                          |        |               |            |
|----------------------------------------------------------|--------|---------------|------------|
| MAD (mothers against<br>decapentaplegic) homolog 3/MADH3 | 603109 | NM_00590<br>2 | 15q21-q22  |
| MAD (mothers against<br>decapentaplegic) homolog 4/MADH4 | 600993 | NM_00535<br>9 | 18q21.1    |
| MAD (mothers against<br>decapentaplegic) homolog 5/MADH5 | 603110 | NM_00590<br>3 | 5q31       |
| MAD (mothers against<br>decapentaplegic) homolog 6/MADH6 | 602931 | NM_00558<br>5 | 15q21-q22  |
| MAD (mothers against<br>decapentaplegic) homolog 7/MADH7 | 602932 | NM_00590<br>4 | Chr.18     |
| MAD (mothers against<br>decapentaplegic) homolog 9/MADH9 | 603295 | NM_00590<br>5 | 13q12-q14  |
| cyclin-dependent kinase (CDK2)                           | 116953 | NM_00179<br>8 | 12q13      |
| cyclin-dependent kinase (CDK3)                           | 123828 | NM_00125<br>8 | 17q22-qter |
| cyclin-dependent kinase (CDK4)                           | 123829 | NM_00007<br>5 | 12q14      |
| cyclin-dependent kinase (CDK5)                           | 123831 | NM_00493<br>5 | 7q36       |
| cyclin-dependent kinase (CDK6)                           | 603368 | NM_00125<br>9 | 7q21-q22   |
| cyclin-dependent kinase (CDK7)                           | 601955 | NM_00315<br>7 | 2p15-cen   |
| cyclin-dependent kinase (CDK8)                           | 603184 | NM_00126<br>0 | 13q12      |
| cyclin-dependent kinase (CDK9)                           | 603251 | NM_00126<br>1 | 9q34.1     |
| cyclin A1                                                | 604036 | U66838        | *****      |
| cyclin A2                                                | 123835 | X51688        | 4q27       |

|                                              |        |               |            |
|----------------------------------------------|--------|---------------|------------|
| cyclin B1                                    | 123836 | M25753        | 5q12       |
| cyclin B2                                    | 602755 | AF002822      | *****      |
| cyclin C                                     | 123838 | M74091        | 6q21       |
| cyclin D1                                    | 168461 | M73554        | 11q13      |
| cyclin D2                                    | 123833 | M90813        | 12p13      |
| cyclin D3                                    | 123834 | M90814        | 6p21       |
| cyclin E1                                    | 123837 | U40739        | 19q13.1    |
| cyclin E2                                    | 603775 | AF091433      | *****      |
| cyclin F                                     | 600227 | Z36714        | 16p13.3    |
| cyclin G1                                    | 601578 | X77794        | 5q32-q34   |
| cyclin G2                                    | 603203 | U47414        | *****      |
| cyclin H                                     | 601953 | U11791        | 5q13.3-q14 |
| cyclin K                                     | 603544 | AF060515      | 14q32      |
| cyclin T1                                    | 602506 | AF045161      | Chr.12     |
| cyclin T2                                    | 603862 | AF048731      | *****      |
| cyclin-dependent kinase inhibitor<br>1a/WAF  | 116899 | U03106        | 6p21.2     |
| cyclin-dependent kinase inhibitor<br>1b/KIP1 | 600778 | U10906        | 12p13      |
| cyclin-dependent kinase inhibitor 2a         | 600160 | NM_00007<br>7 | 9p21       |
| cell cycle CDC2                              | 116940 | NM_00178<br>6 | 10q21.1    |
| cell division cycle 25A/CDC25A               | 116947 | NM_00178<br>9 | 3p21       |
| E2F transcription factor 1/E2F1              | 189971 | M96577        | 20q11.2    |
| E2F transcription factor 2/E2F2              | 600426 | NM_00409<br>1 | 1p36       |
| E2F transcription factor 3/E2F3              | 600427 | NM_00194<br>9 | 6p22       |

## Cell Cycle



|                                                              |        |           |              |
|--------------------------------------------------------------|--------|-----------|--------------|
| E2F transcription factor 4/E2F4                              | 600659 | NM_001950 | 16q22.1      |
| E2F transcription factor 5/E2F5                              | 600967 | NM_001951 | *****        |
| E2F transcription factor 6/E2F6                              | 602944 | NM_001952 | *****        |
| transcription factor Dp-1 (E2F dimerization partner 1)/TFDP1 | 189902 | NM_007111 | 13q34        |
| transcription factor Dp-2 (E2F dimerization partner 2)/TFDP2 | 602160 | NM_006286 | 3q23         |
| retinoblastoma-related gene RB2/p130                         | 180203 | NM_005611 | 16q12.2      |
| retinoblastoma RB1                                           | 180200 | NM_000321 | 13q14.1-14.2 |
| insulin-like growth factor 1/somatomedin C/IGF1              | 147440 | M11568    | 12q22-q24.1  |
| insulin-like growth factor 2/somatomedin A/IGF2              | 147470 | NM_000612 | 11p15.5      |
| insulin-like growth factor binding protein 1                 | 146730 | NM_000596 | 7p14-p12     |
| insulin-like growth factor binding protein 2                 | 146731 | X16302    | 2q33-q34     |
| insulin-like growth factor binding protein 3                 | 146732 | NM_000598 | 7p14-p12     |
| insulin-like growth factor binding protein 4                 | 146733 | M62403    | 17q12-q21    |
| insulin-like growth factor binding protein 5                 | 146734 | L27560    | *****        |
| insulin-like growth factor binding protein 6                 | 146735 | M69054    | Chr.12       |

|                                                    |        |           |               |
|----------------------------------------------------|--------|-----------|---------------|
| insulin-like growth factor binding protein 7       | 602867 | L19182    | 4q12          |
| insulin-like growth factor binding protein 10      | 602369 | U62015    | 1p22.3        |
| schwannoma-derived growth factor/amphiregulin/AREG | 104640 | NM_001657 | 4q13-q21      |
| trefoil factor 1/sP2                               | 113710 | X00474    | 21q22.3       |
| trefoil factor 2/TFF2                              | 182590 | X51698    | 21q22.3       |
| trefoil factor 3/sP2                               | 600633 | L08044    | 21q22.3       |
| epidermal growth factor EGF                        | 131530 | X04571    | 4q25          |
| transforming growth factor (TGF-B1)                | 190180 | M60315    | 19q13.1-q13.3 |
| transforming growth factor (TGF-B2)                | 190220 | M19154    | 1q41          |
| transforming growth factor (TGF-B3)                | 190230 | X14149    | 14q24         |
| vascular endothelial growth factor (VEGF-A)        | 192240 | M32977    | 6p12          |
| vascular endothelial growth factor (VEGF-B)        | 601398 | U52819    | 11q13         |
| vascular endothelial growth factor (VEGF-C)        | 601528 | X94216    | *****         |
| erythropoietin/EPO                                 | 133170 | NM_000799 | 7q21          |
| cardiotrophin 1                                    | 600435 | *****     | *****         |
| leukemia inhibitory factor/LIF                     | 159540 | NM_002309 | 22q12.1-q12.2 |
| ciliary neurotrophic factor/CNTF                   | 118945 | NM_000614 | 11q12.2       |
| oncostatin M                                       | 165095 | *****     | 22q12.1-q12.2 |
| heparin-binding growth factor 1/FGF1               | 131220 | AH002717  | 5q31          |

### Growth Factors

|                                                            |        |           |             |
|------------------------------------------------------------|--------|-----------|-------------|
| basic fibroblast growth factor/FGF2                        | 134920 | M27968    | 4q25-q27    |
| fibroblast growth factor 3/FGF3                            | 164950 | NM_005247 | 11q13       |
| HST oncogene/fibroblast growth factor 4/FGF4               | 164980 | NM_002008 | 11q13       |
| fibroblast growth factor-related protein/FGF5              | 165190 | AH005423  | 4q21        |
| fibroblast growth factor 6/FGF6                            | 134921 | X63454    | 12p13       |
| keratinocyte growth factor/fibroblast growth factor 7/FGF7 | 148180 | L06245    | 15q15-q21.1 |
| fibroblast growth factor 8 (androgen-induced)/FGF8         | 600483 | NM_006119 | 10q24       |
| fibroblast growth factor 9 (glia-activating factor)/FGF9   | 600921 | NM_002010 | 13q11-q12   |
| fibroblast growth factor 10/FGF10                          | 602115 | NM_004465 | 5p13-p12    |
| fibroblast growth factor 11/FGF11                          | 601514 | NM_004112 | 17q21       |
| fibroblast growth factor 12/FGF12                          | 601513 | *****     | 3q28        |
| fibroblast growth factor 13/FGF13                          | 300070 | *****     | Xq26.3      |
| fibroblast growth factor 14/FGF14                          | 601515 | NM_004115 | 13q34       |
| fibroblast growth factor 16/FGF16                          | 603724 | NM_003868 | *****       |
| fibroblast growth factor 17/FGF17                          | 603725 | NM_003867 | 8p21        |
| fibroblast growth factor 18/FGF18                          | 603726 | NM_003862 | *****       |
| fibroblast growth factor 19/FGF19                          | 603891 | NM_005117 | *****       |

|                                                           |        |           |               |
|-----------------------------------------------------------|--------|-----------|---------------|
| stem cell factor/mast cell growth factor (MGF)            | 184745 | NM_003994 | 12q22         |
| thrombopoietin/THPO                                       | 600044 | NM_000460 | 3q26.3-q27    |
| platelet derived growth factor beta polypeptide/PDGFB/SIS | 190040 | NM_002608 | 22q12.3-q13.1 |
| insulin-like growth factor 1 receptor precursor/IGF1R     | 147370 | NM_000875 | 15q25-q26     |
| insulin-like growth factor 2 receptor/IGF2R               | 147280 | NM_000876 | 6q26          |
| epidermal growth factor receptor EGFR                     | 131550 | NM_005228 | 7p12.3-p12.1  |
| tyrosine kinase-type cell surface receptor HER2/ERBB2/NEU | 164870 | X03363    | 17q21.2       |
| glucocorticoid receptor                                   | 138040 | M11050    | 5q31          |
| glucocorticoid receptor alpha                             | 138040 | U25029    | 5q31          |
| glucocorticoid receptor beta                              | 138040 | X03348    | 5q31          |
| progesterone receptor                                     | 264080 | M15716    | 11q22         |
| androgen receptor                                         | 313700 | M20132    | Xq11-q12      |
| estrogen receptor 1 (ESR1)                                | 133430 | M12674    | 6q25.1        |
| estrogen receptor 2 (ESR2)                                | 601663 | X99101    | 14q           |
| retinoic acid receptor alpha (RARA)                       | 180240 | X06538    | 17q12         |
| retinoic acid receptor beta (RARβ)                        | 180220 | X07282    | 3p24          |
| retinoic acid receptor gamma (RARG)                       | 180190 | M38258    | 12q13         |
| Peroxisome proliferative activated receptor, alpha/PPARA  | 170998 | NM_005036 | 22q12-q13.1   |
| Peroxisome proliferative activated receptor, gamma/PPARG  | 601487 | NM_005037 | 3p25          |
| Peroxisome proliferative activated receptor, delta/PPARD  | 180231 | NM_006238 | 1q21.3        |

|                                                        |        |               |                  |
|--------------------------------------------------------|--------|---------------|------------------|
| c-kit (MGF receptor)                                   | 164920 | X06182        | 4q12             |
| TGF-B type I receptor                                  | 190181 | AH006005      | 9q33-q34         |
| TGF-B type II receptor                                 | 190182 | NM_00324<br>2 | 3p22             |
| TGF-B type III receptor                                | 600742 | L07594        | 1p33-p32         |
| fibroblast growth factor receptor<br>1/FGFR1           | 136350 | *****         | 8p11.2-<br>p11.1 |
| fibroblast growth factor receptor<br>2/FGFR2           | 176943 | Y17131        | 10q26            |
| fibroblast growth factor receptor<br>3/FGFR3           | 134934 | NM_00524<br>7 | 4p16.3           |
| fibroblast growth factor receptor<br>4/FGFR4           | 134935 | NM_00201<br>1 | 5q35.1-qter      |
| VEGF receptor                                          | 191306 | X61656        | 4q12             |
| mitogen activated protein kinase<br>PRKM1/MAPK1        | 176948 | NM_00274<br>5 | 22q11.2          |
| mitogen activated protein kinase<br>PRKM3/MAPK3        | 601795 | X60188        | 16p11.2          |
| mitogen activated protein kinase<br>PRKM4/MAPK4        | 176949 | NM_00274<br>7 | 18q12-q21        |
| mitogen activated protein kinase<br>PRKM6/MAPK6        | 602904 | NM_00274<br>8 | *****            |
| mitogen activated protein kinase<br>PRKM7/MAPK7        | 602521 | NM_00274<br>9 | 17p11.2          |
| mitogen activated protein kinase<br>JNK1/PRKM8/MAPK8   | 601158 | L26318        | *****            |
| mitogen activated protein kinase<br>JNK2/PRKM9/MAPK9   | 602896 | U09759        | 5q35             |
| mitogen activated protein kinase<br>JNK3/PRKM10/MAPK10 | 602897 | U35003        | *****            |

|                                                          |        |               |                  |
|----------------------------------------------------------|--------|---------------|------------------|
| mitogen activated protein kinase<br>PRKM11/MAPK11        | 602898 | AF031135      | *****            |
| mitogen activated protein kinase<br>SAPK3/MAPK12         | 602399 | NM_00296<br>9 | 22q13.3          |
| mitogen activated protein kinase<br>PRKM13/MAPK13        | 602899 | NM_00275<br>4 | *****            |
| mitogen activated protein kinase<br>SAPK2A/MAPK14        | 600289 | NM_00131<br>5 | 6p21.3-<br>p21.2 |
| vitamin D3 receptor                                      | 601769 | NM_00037<br>6 | 12q12-q14        |
| transferrin receptor                                     | 190010 | NM_00323<br>4 | 3q29             |
| thyroid stimulating hormone receptor                     | 603372 | NM_00036<br>9 | 14q31            |
| TEK tyrosine kinase receptor (TIE-2)                     | 600221 | X60957        | 9p21             |
| totipotent stem cell receptor FLK 2                      | 600007 | U03858        | *****            |
| leutenizing hormone<br>choriogonadotropin receptor/LHCGR | 152790 | *****         | 2p21             |
| vitamin B12 receptor/cubilin/CUBN                        | 602997 | NM_00108<br>1 | 10p12.1          |
| neurotrophic tyrosine kinase<br>receptor/NTRK1/TRKA      | 191315 | X03541        | 1q21-q22         |
| neurotrophic tyrosine kinase<br>receptor/NTRK2/TRKB      | 600456 | X75958        | 9q22.1           |
| neurotrophic tyrosine kinase<br>receptor/NTRK3/TRKC      | 191316 | U05012        | 15q25            |
| colony stimulating factor 1<br>receptor/CSFR1            | 164770 | U63963        | 5q33.2-<br>q33.3 |

### Receptors

|                                                                                          |        |           |               |
|------------------------------------------------------------------------------------------|--------|-----------|---------------|
| granulocyte-macrophage colony stimulating factor 2 receptor, alpha, low-affinity/CSF2RA  | 306250 | NM_006140 | Xp22.32       |
| granulocyte-macrophage colony stimulating factor 2 receptor, beta/CSF2RB                 | 138981 | U18373    | 22q12.2-q13.1 |
| granulocyte-macrophage colony stimulating factor 2 receptor, alpha, Y chromosomal/CSF2RY | 425000 | *****     | Yp11          |
| MTV oncogene homolog 1/AKT1                                                              | 164730 | K02777    | 14q32.3       |
| MTV oncogene homolog 2/AKT2                                                              | 164731 | NM_001626 | 19q13.1-q13.2 |
| erythropoietin receptor/EPOR                                                             | 133171 | NM_000121 | 19p13.3-p13.2 |
| neutrophil chemotactic response receptor/gp130                                           | 162820 | *****     | 7q22-qter     |
| ciliary neurotrophic factor receptor/CNTFR                                               | 118946 | NM_001842 | 9p13          |
| tumor necrosis factor receptor superfamily, member 1A/TNFRSF1A                           | 191190 | NM_001065 | 12p13.2       |
| tumor necrosis factor receptor superfamily, member 1B/TNFRSF1B                           | 191191 | NM_001066 | 1p36.3-p36.2  |
| tumor necrosis factor receptor superfamily, member 4/TNFRSF4                             | 600315 | NM_003327 | 1p36          |
| tumor necrosis factor receptor superfamily, member 5/TNFRSF5                             | 109535 | NM_001250 | 20q12-q13.2   |
| tumor necrosis factor receptor superfamily, member 6B/TNFRSF6B                           | 603361 | NM_003823 | 20q13         |
| tumor necrosis factor receptor superfamily, member 7/TNFRSF7                             | 186711 | *****     | 12p13         |

|                                                                   |        |               |                  |
|-------------------------------------------------------------------|--------|---------------|------------------|
| tumor necrosis factor receptor<br>superfamily, member 8/TNFRSF8   | 153243 | NM_00124<br>3 | 1p36             |
| tumor necrosis factor receptor<br>superfamily, member 9/TNFRSF9   | 602250 | NM_00156<br>1 | 1p36             |
| superfamily, member<br>10A/TNFRSF10A                              | 603611 | NM_00384<br>4 | 8p21             |
| superfamily, member<br>10B/TNFRSF10B                              | 603612 | NM_00384<br>2 | 8p22-p21         |
| superfamily, member<br>10C/TNFRSF10C                              | 603613 | AF014794      | 8p22-p21         |
| superfamily, member<br>10D/TNFRSF10D                              | 603614 | NM_00384<br>0 | 8p21             |
| superfamily, member<br>11A/TNFRSF11A                              | 603499 | NM_00383<br>9 | 18q22.1          |
| superfamily, member<br>11B/TNFRSF11B                              | 602643 | NM_00254<br>6 | 8q24             |
| tumor necrosis factor receptor<br>superfamily, member 12/TNFRSF12 | 603366 | NM_00379<br>0 | 1p36.3           |
| tumor necrosis factor receptor<br>superfamily, member 14/TNFRSF14 | 602746 | NM_00382<br>0 | 1p36.3-<br>p36.2 |
| tumor necrosis factor receptor<br>superfamily, member 16/TNFRSF16 | 162010 | NM_00250<br>7 | 17q21-q22        |
| tumor necrosis factor receptor<br>superfamily, member 17/TNFRSF17 | 109545 | Z14954        | 16p13.1          |
| tumor necrosis factor receptor<br>superfamily, member 18/TNFRSF18 | 603905 | *****         | 1p36.3           |
| proliferating cell nuclear antigen                                | 176740 | J04718        | 20p12            |
| protein kinase C alpha                                            | 176960 | X52479        | 17q22-<br>q23.2  |
| protein kinase C beta                                             | 176970 | X06318        | 16p11.2          |



|                                                     |        |               |                    |
|-----------------------------------------------------|--------|---------------|--------------------|
| protein kinase C delta                              | 176977 | L07861        | 3p                 |
| protein kinase C gamma                              | 176980 | *****         | 19q13.4            |
| protein kinase C theta                              | 600448 | L01087        | 10p15              |
| protein kinase C zeta                               | 176982 | L14283        | *****              |
| casein kinase 1 alpha 1                             | 600505 | NM_00189<br>2 | 13q13              |
| casein kinase 1 gamma 2                             | 602214 | U89896        | 19p13.3            |
| casein kinase 1 delta                               | 600864 | NM_00189<br>3 | 17q25              |
| casein kinase 1 epsilon                             | 600863 | NM_00189<br>4 | 22q12-q13          |
| casein kinase 2 alpha 1                             | 115440 | J02853        | 20p13              |
| casein kinase 2 alpha 2                             | 115442 | NM_00189<br>6 | 16p13.3-<br>p13.2  |
| casein kinase 2 beta                                | 115441 | X57152        | 6p21.3             |
| mitogen-activated protein kinase<br>kinase 1/MAP2K1 | 176872 | NM_00275<br>5 | 15q22.1-<br>q22.33 |
| mitogen-activated protein kinase<br>kinase 2/MAP2K2 | 601263 | L11285        | *****              |
| mitogen-activated protein kinase<br>kinase 3/MAP2K3 | 602315 | NM_00275<br>6 | 17q11.2            |
| mitogen-activated protein kinase<br>kinase 4/MAP2K4 | 601335 | NM_00301<br>0 | 17p11.2            |
| mitogen-activated protein kinase<br>kinase 5/MAP2K5 | 602520 | NM_00275<br>7 | *****              |
| mitogen-activated protein kinase<br>kinase 6/MAP2K6 | 601254 | U39065        | *****              |
| mitogen-activated protein kinase<br>kinase 7/MAP2K7 | 603014 | NM_00504<br>3 | *****              |
| fos proto-oncogene/FOS                              | 164810 | K00650        | 14q24.3            |

|                                                    |        |           |                |
|----------------------------------------------------|--------|-----------|----------------|
| myc proto-oncogene/MYC                             | 190080 | V00568    | 8q24.12-q24.13 |
| clustrin/TRPM-2                                    | 185430 | M64722    | 8p21-p12       |
| c-jun                                              | 165160 | J04111    | 1p32-p31       |
| c-myb                                              | 189990 | M15024    | 6q22           |
| mdm-2                                              | 164785 | Z12020    | 12q14.3-q15    |
| NF kappaB                                          | 164012 | *****     | 10q24          |
| cAMP-dependent protein kinase/protein kinase A     | 176910 | X14968    | 3p21.3-p21.2   |
| raf-1                                              | 164760 | NM_002880 | 3p25           |
| H-ras                                              | 190020 | J00277    | 11p15.5        |
| K-ras                                              | 190070 | K01912    | 12p12.1        |
| N-ras                                              | 164790 | X02751    | 1p13.2         |
| 1/WT1                                              | 194070 | AH003034  | 11p13          |
| neuroblastoma-derived AMV related oncogene/MYCN    | 164840 | NM_005378 | 2p24.1         |
| GRFS related oncogene/FGR                          | 164940 | NM_005417 | 1p36.2-p36.1   |
| v-abl oncogene homolog 2/ABL2                      | 164690 | M14904    | 1q24-q25       |
| v-abl oncogene homolog 1/ABL1                      | 189980 | U07563    | 9q34.1         |
| murine sarcoma 3611-derived oncogene 1/v-RAF/ARAF1 | 311010 | NM_001654 | Xp11.4-p11.2   |
| murine sarcoma 3611-derived oncogene 2/v-RAF/ARAF2 | 164710 | *****     | 7p11.4-cen     |
| AVE E26 oncogene homolog 1/v-ETS/ETS1              | 164720 | NM_005239 | 11q23.3        |
| AVE E26 oncogene homolog 2/v-ETS/ETS2              | 164740 | M11922    | 21q22.3        |

|                                                        |        |          |       |               |
|--------------------------------------------------------|--------|----------|-------|---------------|
| teratoma oncogene TC21                                 | 60098  | M31470   | ***** | 2q14-q21      |
| liver cancer oncogene/LCO                              | 165320 | *****    |       |               |
| V-FES FSV/V-FPS FASV oncogene homolog/FES              | 190030 | NM_00200 | 5     | 15q26.1       |
| glioma-associated oncogene homolog/GLI                 | 165220 | NM_00526 | 9     | 12q13.2-q13.3 |
| V-CRK ASV CT10 oncogene homolog/CRK                    | 164762 | NM_00520 | 6     | 17p13.3       |
| V-CRK ASV CT10 oncogene homolog-like/CRKL              | 602007 | X59656   |       | 22q11         |
| epithelial cell transforming sequence 2 oncogene/ECT2  | 600586 | *****    |       | 3q26.1-q26.2  |
| V-RAF MSV oncogene homolog B1/BRAF                     | 164757 | AH003899 |       | 7q34          |
| S13 AEV oncogene homolog/SEA                           | 165110 | *****    |       | 11q13         |
| neuroblastoma suppressor/NBS                           | 256700 | NM_00538 | 0     | 1p36.3-p36.2  |
| hepatocyte growth factor receptor/oncogene MET/MET     | 164860 | NM_00024 | 5     | 7q31          |
| MOS oncogene homolog/MOS                               | 190060 | NM_00537 | 2     | 8q11          |
| nuclear receptor coactivator/AIB1                      | 601937 | NM_00653 | 4     | 20q12         |
| signal transducer and activator of transcription/STAT1 | 600555 | M97935   |       | 2q32.2-q32.3  |
| lipocortin 1/annexin 1                                 | 151690 | V00546   |       | 9q11-q22      |
| lipocortin 2/annexin 2                                 | 151740 | D00017   |       | 15q21-q22     |
| lipocortin 3/annexin 3                                 | 106490 | NM_00513 | 9     | 4q21          |

## Signaling

|                                                     |        |           |               |
|-----------------------------------------------------|--------|-----------|---------------|
| AVE E26 oncogene homolog related/ERG                | 165080 | NM_004449 | 21q22.3       |
| AVE E26 oncogene homolog ETS related/ELK1           | 311040 | M25269    | Xp11.2        |
| SFFV virus-induced erythroleukemia oncogene/SP11    | 165170 | NM_003120 | 11p12-p11.22  |
| VAV oncogenem 1/VAV1                                | 164875 | NM_005428 | 19p13.3-p13.2 |
| VAV oncogenem 2/VAV2                                | 600428 | NM_003371 | 9q34          |
| ASV oncogene homolog/SRC                            | 190090 | NM_005417 | 20q12-q13     |
| YSV oncogene homolog 1/YES1                         | 164880 | NM_005433 | 18p11.3       |
| ASV oncogene homolog/SKI                            | 164780 | NM_003036 | 1q22-q24      |
| ASV oncogene homolog-like/SKIL/SNO                  | 165340 | NM_005414 | *****         |
| lung carcinoma-derived AMV oncogene homolog 1/MYCL1 | 164850 | M19720    | 1p34.3        |
| AMV oncogene homolog 1-like/MYCL2                   | 164865 | M64786    | 7p15          |
| MCF.2 cell line-derived transforming sequence/MCF2  | 311030 | J03639    | Xq27          |
| 1/THRA                                              | 190120 | M24898    | 17q11.2       |
| 1/THRB                                              | 190160 | S72623    | 3p24.3        |
| cancer Osaka thyroid (COT) oncogene/COT             | 603259 | D14497    | 10p11.2       |
| CAS-BR-M murine ecotropic retroviral oncogene/CBL   | 165360 | *****     | 11q23.3       |

|                                              |        |               |               |
|----------------------------------------------|--------|---------------|---------------|
| lipocortin 5/annexin 5                       | 131230 | NM_00115<br>4 | 4q26-q28      |
| lipocortin 7/annexin 7 (splice variant 1)    | 186360 | NM_00403<br>4 | 10q21.1-q21.2 |
| lipocortin 7/annexin 7 (splice variant 2)    | 186360 | NM_00115<br>6 | 10q21.1-q21.2 |
| BCL2                                         | 151430 | M13994        | 18q21.3       |
| BCL-X/BCLX                                   | 600039 | Z23115        | *****         |
| BCL2 associated protein/BAX                  | 600040 | L22473        | 19q13.3-q13.4 |
| BCL2-antagonist/killer 1/BAK1                | 600516 | NM_00118<br>8 | 6p21.3-p21.2  |
| BCL2-associated athanogene 1/BAG1            | 601497 | NM_00432<br>3 | 9p12          |
| BCL2-associated athanogene 2/BAG2            | 603882 | NM_00428<br>2 | *****         |
| BCL2-associated athanogene 3/BAG3            | 603883 | AF095193      | *****         |
| BCL2-associated athanogene 4/BAG4            | 603884 | AF095194      | *****         |
| BCL2-associated athanogene 5/BAG5            | 603885 | AF095195      | *****         |
| BCL-X/BCL-2 binding protein/BAD              | 603167 | AF021792      | *****         |
| BCL2-like 1/BCL2L1                           | 600039 | NM_00119<br>1 | *****         |
| BCL2-like 2/BCL2L2                           | 601931 | NM_00405<br>0 | 14q11.2-q12   |
| BCL2-like 11 (apoptosis facilitator)/BCL2L11 | 603827 | NM_00653<br>8 | *****         |
| BCL2-related protein A1/BCL2A1               | 601056 | Y09397        | 15q24.3       |
| BCL2-interacting protein harikari/HRK        | 603447 | NM_00380<br>6 | *****         |
| Bcl-2 interacting killer/BIK                 | 603392 | U34584        | *****         |

|                                                                 |        |               |            |
|-----------------------------------------------------------------|--------|---------------|------------|
| apoptosis inhibitor 1/API1                                      | 601712 | NM_00116<br>6 | 11q22-q23  |
| apoptosis inhibitor 2/API2                                      | 601721 | NM_00116<br>5 | 11q22-q23  |
| apoptosis inhibitor 3/API3                                      | 300079 | NM_00116<br>7 | Xq25       |
| apoptosis inhibitor 4/API4                                      | 603352 | NM_00116<br>8 | *****      |
| secreted apoptosis related protein<br>1/SARP1/SFRP2             | 604157 | AF017986      | 4q31.3     |
| secreted apoptosis related protein<br>2/SARP2/SFRP1             | 604156 | AF017987      | 8p12-p11.1 |
| secreted apoptosis related protein<br>3/SARP3/SFRP5             | 604158 | AF017988      | 10q24.1    |
| programmed cell death 1/PDCD1                                   | 600244 | NM_00501<br>8 | 2q37.3     |
| programmed cell death 2/PDCD2                                   | 600866 | NM_00259<br>8 | 6q27       |
| programmed cell death 8/apoptosis-<br>inducing factor/AIF/PDCD8 | 300169 | NM_00420<br>8 | Xq25-q26   |
| map-kinase activating death<br>domain/DENN                      | 603584 | U44953        | 11p11.2    |
| death-associated protein/DAP                                    | 600954 | NM_00439<br>4 | 5p15.2     |
| death-associated protein kinase<br>1/DAPK1                      | 600831 | NM_00493<br>8 | 9q34.1     |
| death associated protein 3/DAP3                                 | 602074 | NM_00463<br>2 | 1q21       |
| death-associated protein kinase<br>3/DAPK3                      | 603289 | NM_00134<br>8 | 19q13.3    |

|                                                                      |        |               |                    |
|----------------------------------------------------------------------|--------|---------------|--------------------|
| death associated protein<br>6/DAXX/DAP6                              | 603186 | AF050179      | 6p21.3             |
| defender against cell death 1/DAD1                                   | 600243 | NM_00134<br>4 | 14q11-q12          |
| BH3 interacting domain death<br>agonist/BID                          | 601997 | NM_00119<br>6 | 22q11.2            |
| TNF receptor-1 associated<br>protein/TRADD                           | 603500 | L41690        | 16q22              |
| CASP2 and RIPK1 domain containing<br>adaptor with death domain/CRADD | 603454 | NM_00380<br>5 | 12q21.33-<br>q23.1 |
| neuronal apoptosis inhibitory<br>protein/NAIP                        | 600355 | NM_00453<br>6 | 5q12.2-<br>q13.3   |
| RING finger protein/ROC1                                             | 603814 | AF142059      | *****              |
| RING finger protein/ROC2                                             | 603863 | AF142060      | 3q22-q24           |
| tumor protein p53/TP53                                               | 191170 | X02469        | 17p13.1            |
| apoptosis linked gene/calcium binding<br>protein/ALG2                | 601057 | AF035606      | 5p15.2-pter        |
| requiem, apoptosis response zinc<br>finger gene/REQ                  | 601671 | NM_00626<br>8 | 11q13              |
| Fas (TNFRSF6)-associated via death<br>domain/FADD                    | 602457 | NM_00382<br>4 | 11q13.3            |
| chromosome segregation 1 (yeast<br>homolog)-like/CSE1L               | 601342 | NM_00131<br>6 | 20q13              |
| superfamily, member<br>6/FAS/TNFRSF6                                 | 134637 | NM_00004<br>3 | 10q24.1            |
| apoptotic protease activating<br>factor/APAF1                        | 602233 | NM_00116<br>0 | *****              |
| receptor-interacting serine-threonine<br>kinase 1/RIPK1              | 603453 | NM_00380<br>4 | *****              |

|  |                                                        |        |           |                  |
|--|--------------------------------------------------------|--------|-----------|------------------|
|  | receptor-interacting serine-threonine kinase 2/RIPK2   | 603455 | NM_003821 | 8q21             |
|  | apoptosis response protein/PAWR                        | 601936 | NM_002583 | 12q21            |
|  | apoptosis-related cysteine protease 1/caspase 1/CASP1  | 147678 | L27475    | 11q22.2-q22.3    |
|  | apoptosis-related cysteine protease 1/caspase 1/CASP2  | 600639 | *****     | 7q35             |
|  | apoptosis-related cysteine protease 1/caspase 1/CASP3  | 600636 | NM_004346 | 4q35, 4q33-q35.1 |
|  | apoptosis-related cysteine protease 1/caspase 1/CASP4  | 602664 | NM_004347 | 11q22.2-q22.3    |
|  | apoptosis-related cysteine protease 1/caspase 1/CASP5  | 602665 | NM_004347 | 11q22.2-q22.3    |
|  | apoptosis-related cysteine protease 1/caspase 1/CASP6  | 601532 | NM_001226 | 4q25-q25         |
|  | apoptosis-related cysteine protease 1/caspase 1/CASP7  | 601761 | NM_001227 | 10q25.1-q25.2    |
|  | apoptosis-related cysteine protease 1/caspase 1/CASP8  | 601763 | NM_001228 | 2q33-q34         |
|  | apoptosis-related cysteine protease 1/caspase 1/CASP9  | 602234 | *****     | *****            |
|  | apoptosis-related cysteine protease 1/caspase 1/CASP10 | 601762 | NM_001230 | 2q33-q34         |
|  | apoptosis-related cysteine protease 1/caspase 1/CASP13 | 603653 | NM_003723 | *****            |

Table 2. Central Nervous System Gene List

| Class | Pathway | Function | Name | OMIM | GID | Locus |
|-------|---------|----------|------|------|-----|-------|
|-------|---------|----------|------|------|-----|-------|



|                                          |                                                  |        |           |              |
|------------------------------------------|--------------------------------------------------|--------|-----------|--------------|
| Concentration of Transmitter in Vesicles | vacuolar ATPase subunit I                        | 300197 | NM_001183 | *****        |
|                                          | vacuolar ATPase subunit H                        | 603931 | NM_003945 | *****        |
|                                          | vacuolar ATPase subunit D                        | 603097 | NM_004691 | *****        |
|                                          | vacuolar ATPase subunit C                        | 108745 | NM_001694 | 16p13.3      |
|                                          | vacuolar ATPase subunit F                        | 603717 | *****     | *****        |
|                                          | vacuolar ATPase subunit E                        | 108746 | NM_001696 | 22q11.2      |
|                                          | vacuolar ATPase subunit B                        | 192132 | AH007312  | 2cen-q13     |
|                                          | vacuolar ATPase subunit N                        | 192130 | NM_001991 | 17q21        |
|                                          | chromogranin A                                   | 118910 | NM_001275 | 14q32        |
|                                          | chromogranin B                                   | 118920 | NM_001819 | 20pter-p12   |
|                                          | chromogranin C/secretogranin 2                   | 118930 | *****     | 2q35-q36     |
|                                          | carboxypeptidase E/CPE                           | 114855 | NM_001873 | Chr.4        |
|                                          | secretory granule neuroendocrine protein 1/SGNE1 | 173120 | NM_003020 | 15q11-q15    |
|                                          | Nerve growth factor inducible protein/VGF        | 602186 | NM_003378 | 7q22         |
|                                          | neuronal calcium sensor 1/NCS1/frequenin         | 603315 | *****     | *****        |
|                                          | amphiphysin                                      | 600418 | NM_001635 | 7p14-p13     |
|                                          | synapsin 1                                       | 313440 | *****     | Xp11.4-p11.2 |
|                                          | synapsin 2                                       | 600755 | *****     | 3p           |
|                                          | synapsin 3                                       | 602705 | NM_003490 | 22q12.3      |
|                                          | syntaxin 1A                                      | 186590 | D37932    | 7q11.2       |
|                                          | syntaxin 1B                                      | 601485 | *****     | 16p11.2      |
|                                          | syntaxin 3A                                      | 600876 | NM_004177 | *****        |
|                                          | syntaxin 4A                                      | 186591 | NM_004604 | *****        |
|                                          | syntaxin 5A                                      | 603189 | NM_003164 | *****        |
|                                          | syntaxin 6                                       | 603944 | NM_005819 | *****        |
|                                          | syntaxin 7                                       | 603217 | NM_003569 | Chr.6        |
|                                          | syntaxin 10                                      | 603765 | NM_003765 | *****        |

|                                 |        |           |              |
|---------------------------------|--------|-----------|--------------|
| syntaxin 16                     | 603666 | AF038897  | *****        |
| syntaxin binding protein 1      | 602926 | NM_003165 | 9q34.1       |
| syntaxin binding protein 2      | 601717 | U63533    | 9p13.3-p13.2 |
| neurexin 1                      | 600565 | AB011182  | *****        |
| neurexin 2                      | 600566 | *****     | *****        |
| neurexin 3                      | 600567 | NM_004796 | *****        |
| synaptotagmin 1/SYT1            | 185605 | NM_005639 | 12cen-q21    |
| synaptotagmin 2/SYT2            | 600104 | *****     | 1q           |
| synaptotagmin 3/SYT3            | 600327 | *****     | 19q          |
| synaptotagmin 4/SYT4            | 600103 | *****     | 5q           |
| synaptotagmin 5/SYT5            | 600782 | *****     | 11p          |
| synaptobrevin 1/VAMP1           | 185880 | AH002992  | 12p          |
| synaptobrevin 2/VAMP2           | 185881 | AH002993  | 17pter-p12   |
| cellubrevin/VAMP3               | 603657 | *****     | *****        |
| endobrevin/VAMP8                | 603177 | *****     | *****        |
| N-ethylmaleimide sensitive      | 601633 | *****     | 17q21-q22    |
| soluble NSF-attachment protein  |        |           |              |
| gamma/gamma SNAP                | 603216 | NM_003826 | *****        |
| soluble NSF-attachment protein  |        |           |              |
| alpha/alpha SNAP                | 603215 | NM_003827 | *****        |
| synaptosomal-associated protein |        |           |              |
| 23/SNAP23                       | 602534 | NM_003825 | *****        |
| synaptosomal-associated protein |        |           |              |
| 25/SNAP25                       | 600322 | NM_003081 | 20p11.2      |
| Golgi SNARE 27/membrin          | 604027 | NM_004287 | 17q21        |
| Golgi SNARE 28                  | 604026 | *****     | 17q11        |
| secretion deficient 22C         | 604028 | AF039568  | *****        |
| secretion deficient 22L1        | 604029 | NM_004892 | 1q21.2-q21.3 |
| bassoon homolog                 | 604020 | NM_003458 | 3p21.31      |

Neurotransmitter Release

Packaging of Neurotransmitter into Vesicles and Release  
(common to all small molecule neurotransmitters excluding nitric oxide)

|                                                              |        |           |              |
|--------------------------------------------------------------|--------|-----------|--------------|
| voltage-dependent Ca channel L type subunit 1A               | 601011 | NM_000068 | 19p13        |
| voltage-dependent Ca channel N type subunit 1B               | 601012 | NM_000718 | 9q34         |
| voltage-dependent Ca channel L type subunit 1D               | 114206 | NM_000720 | 3p14.3       |
| large conductance Ca-activated K channel M type subunit 1B   | 603951 | NM_004137 | 5q34         |
| large conductance Ca-activated K channel M type subunit 1A   | 600150 | U09384    | Chr.10       |
| RAS-associated protein RAB1                                  | 179508 | NM_004161 | 2p14-p13.4   |
| RAS-associated protein RAB2                                  | 179509 | M28213    | *****        |
| RAS-associated protein RAB3A                                 | 179490 | NM_002866 | 19p13.1-p12  |
| RAS-associated protein RAB3B                                 | 179510 | NM_002867 | 1p32-p31     |
| RAS-associated protein RAB4                                  | 179511 | NM_004578 | 1q42-q43     |
| RAS-associated protein RAB5A                                 | 179512 | NM_004162 | 3p24-p22     |
| RAS-associated protein RAB6                                  | 179513 | NM_002869 | 2q14-q21     |
| agrin                                                        | 103320 | S44195    | 1pter-p32    |
| synaptic vesicle protein 2/SV2                               | 185860 | *****     | *****        |
| synaptic vesicle protein 2B/SV2B                             | 185861 | *****     | *****        |
| axonal transporter of synaptic vesicles/ATSV                 | 601255 | NM_004321 | 2q37         |
| synaptophysin/SVP                                            | 313475 | X06389    | p11.23-p11.2 |
| phosphatidylinositol-4-kinase alpha catalytic subunit/PIK4CA | 600286 | NM_002650 | *****        |
| phosphatidylinositol-4-kinase beta catalytic subunit/PIK4CB  | 602758 | NM_002651 | 1q21.1-q21.3 |
| dynamitin 1/DNMI                                             | 602377 | NM_004408 | 9q34         |
| paired basic amino acid cleaving enzyme/furin/PACE           | 136950 | X04329    | 15q25-q26    |

|                                   |                                                             |        |           |              |
|-----------------------------------|-------------------------------------------------------------|--------|-----------|--------------|
| General<br>Signal<br>Transduction | beta 1 adaptin/ADTB1                                        | 600157 | NM_001127 | 22q12        |
|                                   | beta 3A adaptin/ADTB3A                                      | 603401 | NM_001284 | *****        |
|                                   | gamma adaptin/ADTBG                                         | 603533 | NM_001283 | 16q23        |
|                                   | gamma 2 adaptin/ADPTG2                                      | 603534 | NM_001283 | NM_001283    |
|                                   | human homolog of S. cerevisiae VT11                         | 603207 | AF035824  | *****        |
|                                   | huntingtin (Huntington disease)/HD                          | 143100 | NM_002111 | 4p16.3       |
|                                   | huntingtin-associated protein 1/HAP2                        | 600947 | AF040723  | 17q          |
|                                   | phospholipase C beta 4/PLCB4                                | 600810 | NM_000933 | 20p12        |
|                                   | calmodulin 1/CALM1                                          | 114180 | AH005370  | 14q24-q31    |
|                                   | calmodulin 2/CALM2                                          | 114182 | NM_001743 | 2p21.3-p21.1 |
| Biosynthesis                      | calmodulin 3/CALM3                                          | 114183 | NM_005184 | 9q13.2-q13.3 |
|                                   | calcium/calmodulin dependent protein kinase II alpha/CAMK2A | 114078 | *****     | *****        |
|                                   | calcium/calmodulin dependent protein kinase II gamma/CAMK2G | 602123 | NM_001222 | 10q22        |
|                                   | calcium/calmodulin dependent protein kinase IV/CAMK4        | 114080 | *****     | 5q21-q23     |
|                                   | Glutaminase                                                 | 138280 | AB020645  | 2q32-q34     |
|                                   | Glutamate dehydrogenase 1                                   | 138130 | X07674    | 10q23.3      |
|                                   | Glutamate dehydrogenase 2                                   | 300144 | U08997    | Xq25         |
|                                   | Glutamate Receptor, Ionotropic, Ampa 1; Gria1               | 138248 | M64752    | 5q33         |
|                                   | Glutamate Receptor, Ionotropic, Ampa 2; Gria2               | 138247 | L20814    | 4q32-q33     |
|                                   | Glutamate Receptor, Ionotropic, Ampa 3; Gria3               | 305915 | X82068    | Xq25-q26     |
|                                   | Glutamate Receptor, Ionotropic, Ampa 4; Gria4               | 138246 | NM_000829 | 11q22-q23    |

|                                                            |        |          |              |
|------------------------------------------------------------|--------|----------|--------------|
| Glutamate Receptor, Ionotropic, Delta 2; Grid2             | 602368 | AF009014 | 4q22         |
| Glutamate Receptor, Ionotropic, Kainate 1; Grik1           | 138245 | U16125   | 21q22        |
| Glutamate Receptor, Ionotropic, Kainate 2; Grik2           | 138244 | S75105   | 6q21         |
| Glutamate Receptor, Ionotropic, Kainate 3; Grik3           | 138243 | U16127   | 1p34-p33     |
| Glutamate Receptor, Ionotropic, Kainate 4; Grik4           | 600282 | S67803   | 11q22.3      |
| Glutamate Receptor, Ionotropic, Kainate 5; Grik5           | 600283 | S40369   | 19q13.2      |
| Glutamate Receptor, Ionotropic, N-Methyl-D-Asp 1; Grin1    | 138249 | L13266   | 9q34.3       |
| Glutamate Receptor, Ionotropic, N-Methyl-D-Asp 2a; Grin2a  | 138253 | U09002   | 16p13        |
| Glutamate Receptor, Ionotropic, N-Methyl-D-Asp 2b; Grin2b  | 138252 | U28758   | 12p12        |
| Glutamate Receptor, Ionotropic, N-Methyl-D-Asp 2c; Grin2c  | 138254 | L76224   | 17q25        |
| Glutamate Receptor, Ionotropic, N-Methyl-D-Asp 2d; Grin2d  | 602717 | U77783   | 19q13.1-qter |
| Glutamate Receptor, Ionotropic, N-Methyl-D-Asp A; Grina    | 138251 | *****    | 8q24.3       |
| Glutamate Receptor, Metabotropic 2/G protein-coupled/ Grm2 | 604099 | L35318   | *****        |
| Glutamate Receptor, Metabotropic 3/G protein-coupled/Grm3  | 601115 | X77748   | 7q21.1-q21.2 |
| Glutamate Receptor, Metabotropic 4/G protein-coupled/Grm4  | 604100 | X80818   | *****        |

## Receptors

Glutamate  
(NMDA)  
Pathway

|                     |                                                           |        |           |              |
|---------------------|-----------------------------------------------------------|--------|-----------|--------------|
|                     | Glutamate Receptor, Metabotropic 5/G protein-coupled/Grm5 | 604102 | D28538    | *****        |
|                     | Glutamate Receptor, Metabotropic 6/G protein-coupled/Grm6 | 604096 | U82083    | *****        |
|                     | Glutamate Receptor, Metabotropic 7/G protein-coupled/Grm7 | 604101 | X94552    | *****        |
|                     | Glutamate Receptor, Metabotropic 8/G protein-coupled/Grm8 | 601116 | U95025    | 7q31.3-q32.1 |
|                     | Solute Carrier Family 1, Member 1; Slc1a1                 | 133550 | U08989    | 9p24         |
| <b>Reuptake</b>     | Solute Carrier Family 1, Member 2; Slc1a2                 | 600300 | U03505    | 11p13-p12    |
|                     | Solute Carrier Family 1, Member 3; Slc1a3                 | 600111 | U03504    | 5p13         |
|                     | Glutamine Synthetase                                      | 138290 | X59834    | 1q31         |
| <b>Catabolism</b>   | soluble glutamate oxaloacetate transaminase 1/GOT1        | 138180 | NM_002079 | 0q24.1-q25.1 |
|                     | mitochondrial glutamate oxaloacetate transaminase 2/GOT2  | 138150 | NM_002080 | 16q21        |
|                     | aromatic L-Amino Acid Decarboxylase/AADC                  | 107930 | M76180    | 7p11         |
| <b>Biosynthesis</b> | tryptophan hydroxylase/TPH                                | 191060 | X52836    | 11p15.3-p14  |
|                     | 14-3-3 protein ETA                                        | 113508 | X78138    | 22q12        |
|                     | 14-3-3 protein ZETA                                       | 601288 | M86400    | 2p25.2-p25.1 |
|                     | 14-3-3 protein BETA                                       | 601289 | X57346    | 20q13.1      |
|                     | 14-3-3 protein SIGMA                                      | 601290 | X57348    | *****        |
|                     | serotonin 5-HT receptors 5-HT1A, G protein-coupled        | 109760 | X57829    | 5q11.2-q13   |

|                           |            |                                                    |        |         |              |
|---------------------------|------------|----------------------------------------------------|--------|---------|--------------|
| Serotonin                 | Receptors  | serotonin 5-HT receptors 5-HT1B, G protein-coupled | 182131 | M81590  | 6q13         |
|                           |            | serotonin 5-HT receptors 5-HT1C, G protein-coupled | 312861 | U49516  | Xq24         |
|                           |            | serotonin 5-HT receptors 5-HT1D, G protein-coupled | 182133 | M81590  | 1p36.3-p34.3 |
|                           |            | serotonin 5-HT receptors 5-HT1E, G protein-coupled | 182132 | M91467  | 6q14-q15     |
|                           |            | serotonin 5-HT receptors 5-HT1F, G protein-coupled | 182134 | L05597  | 3p12         |
|                           |            | serotonin 5-HT receptors 5-HT2A, G protein-coupled | 182135 | D87030  | 13q14-q21    |
|                           |            | serotonin 5-HT receptors 5-HT2B, G protein-coupled | 601122 | X77307  | 2q36.3-q37.1 |
|                           |            | serotonin 5-HT receptors 5-HT2C, G protein-coupled | 312861 | U49516  | Xq24         |
|                           |            | serotonin 5-HT receptors 5-HT3, gated ion channel  | 182139 | D49394  | 1q23.1-q23.2 |
|                           |            | serotonin 5-HT receptors 5-HT4, G protein-coupled  | 602164 | Y08756  | 5q31-q33     |
|                           |            | serotonin 5-HT receptors 5-HT5a, G protein-coupled | 601305 | X81411  | 7q36.1       |
|                           |            | serotonin 5-HT receptors 5-HT6, G protein-coupled  | 601109 | L41147  | 1p36-p35     |
|                           |            | serotonin 5-HT receptors 5-HT7, G protein-coupled  | 182137 | L21195  | 10q21-q24    |
|                           | Reuptake   | serotonin transporter                              | 182138 | X70697  | 17q11.1-q12  |
|                           | Catabolism | monoamine oxidase A; MAOA                          | 309850 | M69226  | Xp11.23      |
| monoamine oxidase B; MAOB |            | 309860                                             | M69177 | Xp11.23 |              |

|                                        |                     |            |                                                                   |        |           |               |
|----------------------------------------|---------------------|------------|-------------------------------------------------------------------|--------|-----------|---------------|
| Small<br>Molecule<br>Neurotransmitters | Dopamine<br>Pathway | Catabolism | serotonin N-Acetyltransferase/SNAT                                | 600950 | U40347    | 17q25         |
|                                        |                     |            | tryptophan 2,3-dioxygenase/TDO2                                   | 191070 | NM_005651 | 4q31-q32      |
|                                        | Biosynthesis        |            | Aromatic L-Amino Acid<br>Decarboxylase/AADC/dopa<br>decarboxylase | 107930 | M76180    | 7p11          |
|                                        |                     |            | Tyrosine Hydroxylase                                              | 191290 | X05290    | 11p15.5       |
|                                        |                     |            | Dopamine Receptor D1                                              | 126449 | X58987    | 5q35.1        |
|                                        | Receptors           |            | Dopamine Receptor D2/DRD2                                         | 126450 | NM_000795 | 11q23         |
|                                        |                     |            | Dopamine Receptor D3/DRD3                                         | 126451 | U32499    | 3q13.3        |
|                                        |                     |            | Dopamine Receptor D4                                              | 126452 | L12398    | 11p15.5       |
|                                        |                     |            | Dopamine Receptor D5                                              | 126453 | M67439    | 4p16.1-p15.3  |
|                                        | Reuptake            |            | Dopamine Transporter/ DAT1                                        | 126455 | L24178    | 5p15.3        |
|                                        |                     |            | Dopamine Beta-<br>Hydroxylase/monooxygenase                       | 223360 | Y00096    | 9q34          |
|                                        | Catabolism          |            | Catechol-O-Methyltransferase                                      | 116790 | M58525    | 22q11.2       |
|                                        |                     |            | Monoamine Oxidases A                                              | 309850 | M69226    | Xp11.23       |
|                                        |                     |            | Monoamine Oxidases B                                              | 309860 | M69177    | Xp11.23       |
|                                        |                     |            | Phenol Sulfotransferase 1                                         | 171150 | L10819    | 6p12.1-p11.2  |
|                                        |                     |            | Phenol Sulfotransferase 2                                         | 601292 | X78282    | 16p12.1-p11.2 |
|                                        |                     |            | Phenol Sulfotransferase 3                                         | 600641 | L19956    | 16p11.2       |
|                                        |                     |            | dopamine beta hydroxylase                                         | 223360 | Y00096    | 9q34          |
|                                        | Biosynthesis        |            | phenylethanolamine-N-<br>tyrosine Hydroxylase                     | 171190 | NM_002686 | 17q21-q22     |
|                                        |                     |            | tyrosine Hydroxylase                                              | 191290 | X05290    | 11p15.5       |
|                                        |                     |            | alpha-1a-adrenergic receptor;                                     | 104219 | M76446    | Chr.20        |
|                                        |                     |            | alpha-1b-adrenergic receptor;                                     | 104220 | L31773    | 5q33          |
|                                        |                     |            | alpha-1c-adrenergic receptor;                                     | 104221 | D25235    | 8p21          |
|                                        |                     |            | alpha-1d-adrenergic receptor;                                     | 104222 | M76446    | 20p13         |
|                                        |                     |            | alpha-2a-adrenergic receptor;                                     | 104210 | M18415    | 10q24-q26     |
|                                        |                     |            | alpha-2b-adrenergic receptor;                                     | 104260 | AF005900  | Chr.2         |



|                                                           |                     |                                                       |        |           |            |
|-----------------------------------------------------------|---------------------|-------------------------------------------------------|--------|-----------|------------|
| <b>Epinephrine<br/>and<br/>Norepinephrine<br/>Pathway</b> | <b>Receptors</b>    | alpha-2c-adrenergic receptor;                         | 104250 | J03853    | 4q16.1     |
|                                                           |                     | beta-1-adrenergic receptor; Adrb1                     | 109630 | J03019    | 10q24-q26  |
|                                                           |                     | Beta-2-Adrenergic Receptor; Adrb2                     | 109690 | M15169    | 5q32-q34   |
|                                                           |                     | beta-adrenergic receptor kinase                       |        |           |            |
|                                                           |                     | 1/BARK1                                               | 109635 | NM_001619 | 11cen-q13  |
|                                                           |                     | Beta-2-Adrenergic Receptor-Like<br>Protein G-21       | 109760 | X57829    | 5q11.2-q13 |
|                                                           |                     | Beta-3-Adrenergic Receptor; Adrb3                     | 109691 | X70811    | 8p12-p11.2 |
|                                                           |                     | Beta-Adrenergic Receptor Kinase 1;<br>Adrbk1          | 109635 | X61157    | 11cen-q13  |
|                                                           |                     | Beta-Adrenergic Receptor Kinase 2;<br>Adrbk2          | 109636 | X69117    | 22q11      |
|                                                           |                     | Vesicular Amine Transporter 2; VAT2                   | 193001 | L09118    | 10q25      |
|                                                           | <b>Reuptake</b>     | Vesicular Amine Transporter 1; VAT1                   | 193002 | *****     | 8p21.3     |
|                                                           |                     | Solute carrier family 6, member<br>5/SLC6A2/NAT1/NET1 | 163970 | NM_001043 | 16q12.2    |
|                                                           | <b>Catabolism</b>   | Monoamine Oxidase A; MAOA                             | 309850 | M69226    | Xp11.23    |
|                                                           |                     | Monoamine Oxidase B; MAOB                             | 309860 | M69177    | Xp11.23    |
|                                                           |                     | Catechol-O-Methyltransferase                          | 116790 | M58525    | 22q11.2    |
|                                                           |                     | Choline acetyltransferase/CHAT                        | 118490 | NM_003055 | 10q11.2    |
|                                                           | <b>Biosynthesis</b> | carnitine acetyltransferase/CRAT                      | 600184 | NM_004003 | 9q34.1     |
|                                                           |                     | apolipoprotein E                                      | 107741 | NM_000041 | 19q13.2    |
|                                                           |                     | Cholinergic Receptor, Muscarinic, 1;<br>CHRM1         | 118510 | X15263    | 11q13      |
|                                                           |                     | Cholinergic Receptor, Muscarinic, 2;<br>CHRM2         | 118493 | U19800    | 7q35-q36   |
|                                                           |                     | Cholinergic Receptor, Muscarinic, 3;<br>CHRM3         | 118494 | U29589    | 1q41-q44   |

|                              |                     |                                                      |        |           |               |
|------------------------------|---------------------|------------------------------------------------------|--------|-----------|---------------|
| <b>Acetylcholine Pathway</b> | <b>Receptors</b>    | Cholinergic Receptor, Muscarinic, 4; CHRM4           | 118495 | M16405    | 11p12-p11.2   |
|                              |                     | Cholinergic Receptor, Muscarinic, 5; CHRM5           | 118496 | AF026263  | 15q26         |
|                              |                     | Nicotinic, Cholinergic receptor alpha 1              | 100690 | X70108    | 2q24-q32      |
|                              |                     | Nicotinic, Cholinergic receptor alpha 2              | 118502 | U62431    | Chr.8         |
|                              |                     | Nicotinic, Cholinergic receptor alpha 3              | 118503 | X53559    | 15q24         |
|                              |                     | Nicotinic, Cholinergic receptor alpha 4              | 118504 | U62433    | 20q13.2-q13.3 |
|                              |                     | Nicotinic, Cholinergic receptor alpha 5              | 118505 | M83712    | 15q24         |
|                              |                     | Nicotinic, Cholinergic receptor alpha 7/CHRNA7       | 118511 | U40583    | 15q14         |
|                              |                     | Nicotinic, Cholinergic receptor beta 1               | 100710 | X14830    | 17p12-p11     |
|                              |                     | Nicotinic, Cholinergic receptor beta 2               | 118507 | Y08415    | 1p21          |
|                              | <b>Reuptake</b>     | Nicotinic, Cholinergic receptor beta 3               | 118508 | X67513    | 8p11.2        |
|                              |                     | Nicotinic, Cholinergic receptor beta 4               | 118509 | X68275    | 15q24         |
|                              |                     | Nicotinic, Cholinergic receptor epsilon polypeptide  | 100725 | X66403    | Chr.17        |
|                              |                     | Nicotinic, Cholinergic receptor,                     | 100720 | X55019    | 2q33-q34      |
|                              |                     | Nicotinic, Cholinergic receptor,                     | 100730 | NM_005199 | 2q33-q34      |
|                              |                     | Vesicular acetylcholine transporter                  | 600336 | NM_003055 | 10q11.2       |
|                              | <b>Catabolism</b>   | Acetylcholinesterase/ACHE                            | 100740 | M55040    | 7q22          |
|                              |                     | butyrylcholinesterase 1/serum cholinesterase 1/BCHE1 | 177400 | NM_000055 | 3q26.1-q26.2  |
|                              |                     | butyrylcholinesterase 2/serum cholinesterase 2/BCHE2 | 177500 | *****     | 2q33-q35      |
|                              |                     | Histidine Decarboxylase                              | 142704 | M60445    | 15q21-q22     |
|                              | <b>Biosynthesis</b> | histamine H1 receptor/HRH1                           | 600167 | NM_000861 | 3p21-p14      |
|                              |                     | histamine H2 receptor/HRH2                           | 142703 | AB023486  | *****         |
|                              | <b>Receptors</b>    |                                                      |        |           |               |

| Histaminergic Pathway | histamine H3 receptor/HRH3                                      | *****  | NM_00723<br>2 | *****         |
|-----------------------|-----------------------------------------------------------------|--------|---------------|---------------|
|                       |                                                                 | *****  | NM_006895     | chr. 2        |
| Catabolism            | Histamine N-                                                    |        |               |               |
|                       | Amine oxidase (copper-containing)<br>2/AOC2                     | 602268 | D88213        | 17q21         |
|                       | Amine oxidase (copper-containing)<br>3/AOC3                     | 603735 | AF054985      | 17q21         |
| Biosynthesis          | adenylosuccinate lyase/ADSL                                     | 103050 | NM_000026     | 22q13.1       |
|                       | adenylosuccinate synthetase/ADSS                                | 103060 | NM_001126     | 1cen-q12      |
|                       | Adenosine A1 Receptor; Adora1/G<br>protein-coupled              | 102775 | L22214        | 1q32.1        |
| Adenosine Pathway     | Adenosine A2 Receptor; Adora2a/G<br>protein-coupled             | 102776 | X68486        | 22q11.2       |
|                       | Adenosine A2b Receptor; Adora2b/G<br>protein-coupled            | 600446 | X68487        | 17p12-p11.2   |
|                       | Adenosine A3 Receptor; Adora3/G<br>protein-coupled              | 600445 | L20463        | 1p21-p13      |
|                       | Adenosine A2 Receptor-<br>like/ADORA2L1                         | 102777 | *****         | 10q25.3-q26.1 |
|                       | Purinergic Receptor P2x, Ligand-<br>Gated Ion Channel, 1; P2rx1 | 600845 | NM_002558     | *****         |
|                       | Purinergic Receptor P2x, Ligand-<br>Gated Ion Channel, 3; P2rx3 | 600843 | Y07683        | 11q12         |
|                       | Purinergic Receptor P2x, Ligand-<br>Gated Ion Channel, 4; P2rx4 | 600846 | AF000234      | 12q24.32      |
|                       | Purinergic Receptor P2x, Ligand-<br>Gated Ion Channel, 5; P2rx5 | 602836 | NM_002561     | *****         |
|                       | Purinergic Receptor P2x, Ligand-<br>Gated Ion Channel, 7; P2rx7 | 602566 | Y09561        | 12q24         |
|                       | Receptors                                                       |        |               |               |

|  |                                                                          |        |           |              |
|--|--------------------------------------------------------------------------|--------|-----------|--------------|
|  | P2Y11 purinoceptor/G protein-receptor/G protein-coupled                  | 602697 | *****     | *****        |
|  | P2Y7 purinoceptor/leukotriene B4 receptor/G protein-coupled              | 601531 | NM_000752 | 14q11.2-q12  |
|  | P2Y2 purinoceptor/G protein-coupled                                      | 600041 | U07225    | 1q13.5-q14.1 |
|  | P2Y1 purinoceptor/G protein-coupled                                      | 601167 | U42029    | 3q25         |
|  | P2Y4 pyrimidinergic receptor/G protein-coupled                           | 300038 | NM_002565 | Xq13         |
|  | P2Y6 pyrimidinergic receptor/purinoreceptor P2Y6/G protein-coupled/P2RY6 | 602451 | NM_004154 | 11q13.5      |
|  | Solute carrier family 29 (nucleosides), member 1/SLC29A1/ENT1            | 602193 | NM_004955 | 6p21.2-p21.1 |
|  | Solute carrier family 29 (nucleosides), member 2/SLC29A2/ENT2            | 602110 | X86681    | 11q13        |
|  | adenosine deaminase                                                      | 102700 | NM_000022 | 20q13.11     |
|  | Glutamate decarboxylase 1 (brain, 67kD)                                  | 266100 | M81883    | 2q31         |
|  | Glutamate decarboxylase 2 (brain, 65kD)                                  | 138275 | X69936    | 10p11.23     |
|  | Glutamate decarboxylase 3                                                | 138276 | 138276    | 22q13        |
|  | Gamma-Aminobutyric Acid Receptor, Beta-3; Gabrb3                         | 137192 | M82919    | 15q11.2-q12  |
|  | Gamma-Aminobutyric Acid Receptor, Alpha-3; Gabra3                        | 305660 | S62908    | Xq28         |
|  | Gamma-Aminobutyric Acid Receptor, Alpha-5; Gabra5                        | 137142 | L08485    | 15q11.2-q12  |
|  | Gamma-Aminobutyric Acid Receptor, Alpha-1; Gabral                        | 137160 | X14766    | 5q34-q35     |

|                                                                    |        |           |              |
|--------------------------------------------------------------------|--------|-----------|--------------|
| Gamma-Aminobutyric Acid Receptor, Alpha-6; Gabra6                  | 137143 | S81944    | 5q31.1-q35   |
|                                                                    | 603540 | Y11044    | *****        |
|                                                                    | 137140 | S62907    | 4p13-p12     |
|                                                                    | 600233 | NM_000816 | 15q11.2-q12  |
|                                                                    | 137190 | X14767    | 4p13-p12     |
|                                                                    | 602729 | U95367    | *****        |
|                                                                    | 300093 | Y09765    | Xq28         |
|                                                                    | 137141 | U30461    | 4p14-q12     |
|                                                                    | 600232 | S77553    | 5q34-q35     |
|                                                                    | 137164 | X15376    | 5q31.1-q33.1 |
|                                                                    | 137166 | *****     | 4p14-q21.1   |
|                                                                    | 137163 | AF016917  | 1p           |
|                                                                    | 137161 | M62400    | 6q14-q21     |
|                                                                    | 137162 | M86868    | 6q14-q21     |
|                                                                    | 109610 | NM_000714 | 22q13.31     |
|                                                                    | 125950 | M15887    | 2q12-q21     |
| Gamma-Aminobutyric Acid Receptor, Alpha-2; Gabra2                  | 137143 | S81944    | 5q31.1-q35   |
|                                                                    | 603540 | Y11044    | *****        |
|                                                                    | 137140 | S62907    | 4p13-p12     |
|                                                                    | 600233 | NM_000816 | 15q11.2-q12  |
|                                                                    | 137190 | X14767    | 4p13-p12     |
|                                                                    | 602729 | U95367    | *****        |
|                                                                    | 300093 | Y09765    | Xq28         |
|                                                                    | 137141 | U30461    | 4p14-q12     |
|                                                                    | 600232 | S77553    | 5q34-q35     |
|                                                                    | 137164 | X15376    | 5q31.1-q33.1 |
|                                                                    | 137166 | *****     | 4p14-q21.1   |
|                                                                    | 137163 | AF016917  | 1p           |
|                                                                    | 137161 | M62400    | 6q14-q21     |
|                                                                    | 137162 | M86868    | 6q14-q21     |
|                                                                    | 109610 | NM_000714 | 22q13.31     |
|                                                                    | 125950 | M15887    | 2q12-q21     |
| Gamma-Aminobutyric Acid Receptor, Beta-1; Gabrb1                   | 137143 | S81944    | 5q31.1-q35   |
|                                                                    | 603540 | Y11044    | *****        |
|                                                                    | 137140 | S62907    | 4p13-p12     |
|                                                                    | 600233 | NM_000816 | 15q11.2-q12  |
|                                                                    | 137190 | X14767    | 4p13-p12     |
|                                                                    | 602729 | U95367    | *****        |
|                                                                    | 300093 | Y09765    | Xq28         |
|                                                                    | 137141 | U30461    | 4p14-q12     |
|                                                                    | 600232 | S77553    | 5q34-q35     |
|                                                                    | 137164 | X15376    | 5q31.1-q33.1 |
|                                                                    | 137166 | *****     | 4p14-q21.1   |
|                                                                    | 137163 | AF016917  | 1p           |
|                                                                    | 137161 | M62400    | 6q14-q21     |
|                                                                    | 137162 | M86868    | 6q14-q21     |
|                                                                    | 109610 | NM_000714 | 22q13.31     |
|                                                                    | 125950 | M15887    | 2q12-q21     |
| Gamma-Aminobutyric Acid Receptor, Gamma-1; Gabrg1                  | 137143 | S81944    | 5q31.1-q35   |
|                                                                    | 603540 | Y11044    | *****        |
|                                                                    | 137140 | S62907    | 4p13-p12     |
|                                                                    | 600233 | NM_000816 | 15q11.2-q12  |
|                                                                    | 137190 | X14767    | 4p13-p12     |
|                                                                    | 602729 | U95367    | *****        |
|                                                                    | 300093 | Y09765    | Xq28         |
|                                                                    | 137141 | U30461    | 4p14-q12     |
|                                                                    | 600232 | S77553    | 5q34-q35     |
|                                                                    | 137164 | X15376    | 5q31.1-q33.1 |
|                                                                    | 137166 | *****     | 4p14-q21.1   |
|                                                                    | 137163 | AF016917  | 1p           |
|                                                                    | 137161 | M62400    | 6q14-q21     |
|                                                                    | 137162 | M86868    | 6q14-q21     |
|                                                                    | 109610 | NM_000714 | 22q13.31     |
|                                                                    | 125950 | M15887    | 2q12-q21     |
| Gamma-Aminobutyric Acid Receptor, Delta; Gabrd                     | 137143 | S81944    | 5q31.1-q35   |
|                                                                    | 603540 | Y11044    | *****        |
|                                                                    | 137140 | S62907    | 4p13-p12     |
|                                                                    | 600233 | NM_000816 | 15q11.2-q12  |
|                                                                    | 137190 | X14767    | 4p13-p12     |
|                                                                    | 602729 | U95367    | *****        |
|                                                                    | 300093 | Y09765    | Xq28         |
|                                                                    | 137141 | U30461    | 4p14-q12     |
|                                                                    | 600232 | S77553    | 5q34-q35     |
|                                                                    | 137164 | X15376    | 5q31.1-q33.1 |
|                                                                    | 137166 | *****     | 4p14-q21.1   |
|                                                                    | 137163 | AF016917  | 1p           |
|                                                                    | 137161 | M62400    | 6q14-q21     |
|                                                                    | 137162 | M86868    | 6q14-q21     |
|                                                                    | 109610 | NM_000714 | 22q13.31     |
|                                                                    | 125950 | M15887    | 2q12-q21     |
| Gamma-Aminobutyric Acid Receptor, Gamma-2; Gabrg2                  | 137143 | S81944    | 5q31.1-q35   |
|                                                                    | 603540 | Y11044    | *****        |
|                                                                    | 137140 | S62907    | 4p13-p12     |
|                                                                    | 600233 | NM_000816 | 15q11.2-q12  |
|                                                                    | 137190 | X14767    | 4p13-p12     |
|                                                                    | 602729 | U95367    | *****        |
|                                                                    | 300093 | Y09765    | Xq28         |
|                                                                    | 137141 | U30461    | 4p14-q12     |
|                                                                    | 600232 | S77553    | 5q34-q35     |
|                                                                    | 137164 | X15376    | 5q31.1-q33.1 |
|                                                                    | 137166 | *****     | 4p14-q21.1   |
|                                                                    | 137163 | AF016917  | 1p           |
|                                                                    | 137161 | M62400    | 6q14-q21     |
|                                                                    | 137162 | M86868    | 6q14-q21     |
|                                                                    | 109610 | NM_000714 | 22q13.31     |
|                                                                    | 125950 | M15887    | 2q12-q21     |
| Gamma-Aminobutyric Acid Receptor, Epsilon; Gabre                   | 137143 | S81944    | 5q31.1-q35   |
|                                                                    | 603540 | Y11044    | *****        |
|                                                                    | 137140 | S62907    | 4p13-p12     |
|                                                                    | 600233 | NM_000816 | 15q11.2-q12  |
|                                                                    | 137190 | X14767    | 4p13-p12     |
|                                                                    | 602729 | U95367    | *****        |
|                                                                    | 300093 | Y09765    | Xq28         |
|                                                                    | 137141 | U30461    | 4p14-q12     |
|                                                                    | 600232 | S77553    | 5q34-q35     |
|                                                                    | 137164 | X15376    | 5q31.1-q33.1 |
|                                                                    | 137166 | *****     | 4p14-q21.1   |
|                                                                    | 137163 | AF016917  | 1p           |
|                                                                    | 137161 | M62400    | 6q14-q21     |
|                                                                    | 137162 | M86868    | 6q14-q21     |
|                                                                    | 109610 | NM_000714 | 22q13.31     |
|                                                                    | 125950 | M15887    | 2q12-q21     |
| Gamma-Aminobutyric Acid Receptor, Alpha-4; Gabra4                  | 137143 | S81944    | 5q31.1-q35   |
|                                                                    | 603540 | Y11044    | *****        |
|                                                                    | 137140 | S62907    | 4p13-p12     |
|                                                                    | 600233 | NM_000816 | 15q11.2-q12  |
|                                                                    | 137190 | X14767    | 4p13-p12     |
|                                                                    | 602729 | U95367    | *****        |
|                                                                    | 300093 | Y09765    | Xq28         |
|                                                                    | 137141 | U30461    | 4p14-q12     |
|                                                                    | 600232 | S77553    | 5q34-q35     |
|                                                                    | 137164 | X15376    | 5q31.1-q33.1 |
|                                                                    | 137166 | *****     | 4p14-q21.1   |
|                                                                    | 137163 | AF016917  | 1p           |
|                                                                    | 137161 | M62400    | 6q14-q21     |
|                                                                    | 137162 | M86868    | 6q14-q21     |
|                                                                    | 109610 | NM_000714 | 22q13.31     |
|                                                                    | 125950 | M15887    | 2q12-q21     |
| Gamma-Aminobutyric Acid Receptor, Beta-2; Gabrb2                   | 137143 | S81944    | 5q31.1-q35   |
|                                                                    | 603540 | Y11044    | *****        |
|                                                                    | 137140 | S62907    | 4p13-p12     |
|                                                                    | 600233 | NM_000816 | 15q11.2-q12  |
|                                                                    | 137190 | X14767    | 4p13-p12     |
|                                                                    | 602729 | U95367    | *****        |
|                                                                    | 300093 | Y09765    | Xq28         |
|                                                                    | 137141 | U30461    | 4p14-q12     |
|                                                                    | 600232 | S77553    | 5q34-q35     |
|                                                                    | 137164 | X15376    | 5q31.1-q33.1 |
|                                                                    | 137166 | *****     | 4p14-q21.1   |
|                                                                    | 137163 | AF016917  | 1p           |
|                                                                    | 137161 | M62400    | 6q14-q21     |
|                                                                    | 137162 | M86868    | 6q14-q21     |
|                                                                    | 109610 | NM_000714 | 22q13.31     |
|                                                                    | 125950 | M15887    | 2q12-q21     |
| Gamma-Aminobutyric Acid Receptor, Gamma-3; Gabrg3                  | 137143 | S81944    | 5q31.1-q35   |
|                                                                    | 603540 | Y11044    | *****        |
|                                                                    | 137140 | S62907    | 4p13-p12     |
|                                                                    | 600233 | NM_000816 | 15q11.2-q12  |
|                                                                    | 137190 | X14767    | 4p13-p12     |
|                                                                    | 602729 | U95367    | *****        |
|                                                                    | 300093 | Y09765    | Xq28         |
|                                                                    | 137141 | U30461    | 4p14-q12     |
|                                                                    | 600232 | S77553    | 5q34-q35     |
|                                                                    | 137164 | X15376    | 5q31.1-q33.1 |
|                                                                    | 137166 | *****     | 4p14-q21.1   |
|                                                                    | 137163 | AF016917  | 1p           |
|                                                                    | 137161 | M62400    | 6q14-q21     |
|                                                                    | 137162 | M86868    | 6q14-q21     |
|                                                                    | 109610 | NM_000714 | 22q13.31     |
|                                                                    | 125950 | M15887    | 2q12-q21     |
| Benzodiazepine receptor, peripheral diazepam binding inhibitor/DBI | 137143 | S81944    | 5q31.1-q35   |
|                                                                    | 603540 | Y11044    | *****        |
|                                                                    | 137140 | S62907    | 4p13-p12     |
|                                                                    | 600233 | NM_000816 | 15q11.2-q12  |
|                                                                    | 137190 | X14767    | 4p13-p12     |
|                                                                    | 602729 | U95367    | *****        |
|                                                                    | 300093 | Y09765    | Xq28         |
|                                                                    | 137141 | U30461    | 4p14-q12     |
|                                                                    | 600232 | S77553    | 5q34-q35     |
|                                                                    | 137164 | X15376    | 5q31.1-q33.1 |
|                                                                    | 137166 | *****     | 4p14-q21.1   |
|                                                                    | 137163 | AF016917  | 1p           |
|                                                                    | 137161 | M62400    | 6q14-q21     |
|                                                                    | 137162 | M86868    | 6q14-q21     |
|                                                                    | 109610 | NM_000714 | 22q13.31     |
|                                                                    | 125950 | M15887    | 2q12-q21     |

## Receptors

Gamma-Aminobutyric Acid Pathway

|                        |                     |                                                         |        |           |              |
|------------------------|---------------------|---------------------------------------------------------|--------|-----------|--------------|
|                        | <b>Reuptake</b>     | Solute carrier family 6 (GABA), member 1/SLC6A1         | 137165 | X54673    | 3p25-p24     |
|                        |                     | Solute carrier family 1, member 6 (GABA/GLU)/SLC1A6     | 600637 | NM_005071 | *****        |
|                        |                     | Solute carrier family 6 (betaine/GABA), member 12       | 603080 | U27699    | 12p13        |
|                        |                     | GABA-glutamate transaminase                             | 137150 | NM_000663 | *****        |
|                        | <b>Catabolism</b>   | succinic semialdehyde dehydrogenase/SSADH               | 271980 | NM_001080 | 6p22         |
|                        |                     | Sacrosine dehydrogenase                                 | 268900 | *****     | 9q33-q34     |
|                        |                     | Alanine-glyoxylate aminotransferase, cytosolic serine   | 259900 | NM_000030 | 2q36-q37     |
|                        |                     | hydroxymethyltransferase 1/SHMT1 mitochondrial serine   | 182144 | NM_004169 | 17p11.2      |
|                        | <b>Biosynthesis</b> | hydroxymethyltransferase 2/SHMT2                        | 138450 | *****     | 12q13        |
|                        |                     | Glycine Receptor, Alpha-1 Subunit; Glra1                | 138491 | X52009    | 5q32         |
|                        |                     | Glycine Receptor, Alpha-2 Subunit; Glra2                | 305990 | X52008    | Xp22.1-p21.2 |
|                        |                     | Glycine Receptor, Alpha-3 Subunit; Glra3                | 600421 | AF018157  | 4q33-q34     |
|                        | <b>Receptors</b>    | Glycine Receptor, Beta Subunit; Glrb                    | 138492 | U33267    | 4q31.3       |
|                        |                     | Solute carrier family 6, Member 9; SLC6A9 (glycine)     | 601019 | S70612    | 1p33         |
|                        |                     | Solute carrier family 6, Member 5; SLC6A5 (glycine)     | 604159 | NM_004211 | *****        |
|                        |                     | Glycine aminotransferase/glycine cleavage T protein/GAT | 238310 | NM_000481 | 3p21.2-p21.1 |
| <b>Glycine Pathway</b> |                     |                                                         |        |           |              |

|                             |                     |                                                              |        |           |              |
|-----------------------------|---------------------|--------------------------------------------------------------|--------|-----------|--------------|
|                             | <b>Catabolism</b>   | Glycine dehydrogenase/glycine cleavage P protein             | 238300 | M63635    | 9p22         |
|                             |                     | Aminomethyl carrier/glycine cleavage H protein               | 238330 | NM_004483 | *****        |
|                             |                     | Dihydroliipoamide dehydrogenase/glycine cleavage L           | 238331 | *****     | *****        |
| <b>Taurine</b>              | <b>Biosynthesis</b> | cysteine dioxygenase, type I/CDO1                            | 603943 | NM_001801 | 5q22-q23     |
|                             |                     | sulfite oxidase/SUOX                                         | 272300 | NM_000456 | *****        |
| <b>Melatonin</b>            | <b>Receptors</b>    | solute carrier family 6, member 6/taurine transporter/SLC6A6 | 186854 | U16120    | 3p25-q24     |
|                             |                     | serotonin N-Acetyltransferase/SNAT                           | 600950 | U40347    | 17q25        |
|                             | <b>Biosynthesis</b> | X-chromosomal acetylserotonin N-methyltransferase/ASMT       | 300015 | NM_004043 | Xpter-p22.32 |
|                             |                     | Y-chromosomal acetylserotonin N-methyltransferase/ASMT       | 402500 | *****     | Ypter-p11.2  |
|                             |                     | acetylserotonin N-methyltransferase-like/ASMTL               | 300162 | NM_004192 | Xpter-p22.32 |
|                             |                     | melatonin receptor 1A/MTNR1A                                 | 600665 | NM_005958 | 4q35.1       |
|                             | <b>Receptors</b>    | melatonin receptor 1B/MTNR1B                                 | 600804 | NM_005959 | 11q21-q22    |
|                             |                     | tryptophan 2,3-dioxygenase/TDO2                              | 191070 | NM_005651 | 4q31-q32     |
|                             | <b>Catabolism</b>   | nitric oxide synthetase 1/NOS1                               | 163731 | AH001515  | 2q24.2-q24.3 |
|                             |                     | nitric oxide synthetase 2A/NOS2A                             | 163730 | X85766    | 17cen-q11.2  |
| <b>Nitric Oxide Pathway</b> | <b>Biosynthesis</b> | macrophage nitric oxide synthetase 2B/NOS2B                  | 600719 | AH006623  | 17p13.1-q25  |
|                             |                     | macrophage nitric oxide synthetase 2C/NOS2C                  | 600720 | 600720    | 17p13.1-q25  |
|                             |                     | nitric oxide synthetase 3/NOS3                               | 163729 | AH001515  | 7q36         |
|                             |                     | chondrocyte nitric oxide synthetase 3/NOS4                   | 163728 | X73029    | *****        |

|  |  |                                                 |        |           |              |
|--|--|-------------------------------------------------|--------|-----------|--------------|
|  |  | arginase/ARG1                                   | 207800 | NM_000045 | *****        |
|  |  | arginase/ARG2                                   | 107830 | NM_001172 | 4q24.1-q24.2 |
|  |  | membrane                                        |        |           |              |
|  |  | metalloendopeptidase/MME/neutral                |        |           |              |
|  |  | endopeptidase                                   | 120520 | AH002677  | 3q21-q27     |
|  |  | calpain, large polypeptide L3/CAPN3             | 114240 | NM_000070 | 5q15.1-q21.1 |
|  |  | Leucyl/cystinyl aminopeptidase                  | 151300 | U62768    | *****        |
|  |  | carboxypeptidase N polypeptide                  |        |           |              |
|  |  | 1/CPN1                                          | 603103 | NM_001308 | chr. 10      |
|  |  | carboxypeptidase N polypeptide                  |        |           |              |
|  |  | 2/regulatory subunit/CPN2                       | 603104 | J05158    | 8p23-p22     |
|  |  | meprin alpha subunit/MEP1A                      | 600388 | NM_005925 | 6p21.2-p21.1 |
|  |  | meprin beta subunit/MEP1B                       | 600389 | NM_005925 | 8q12.2-q12.3 |
|  |  | prolyl endopeptidase/PREP                       | 600400 | NM_002726 | 6q22         |
|  |  | neuroendocrine convertase 1/NEC1                | 162150 | D73407    | 5q14-q21     |
|  |  | peptidylglycine alpha-amidating                 |        |           |              |
|  |  | monooxygenase /PAM/NEC2                         | 170270 | NM_000919 | 5q14-q21     |
|  |  | paired basic amino acid cleaving                |        |           |              |
|  |  | enzyme/PACE/FUR                                 | 136950 | X04329    | 15q25-q26    |
|  |  | proopiomelanocortin                             | 176830 | NM_000939 | 2p23.3       |
|  |  | prepronociceptin/nociceptin/hosistatin/<br>PNOC | 601459 | *****     | 8p21         |
|  |  | preproenkephalin                                |        |           |              |
|  |  | B/prodynorphin/PDYN                             | 131340 | NM_006211 | 12p12.21     |
|  |  | preproenkephalin                                |        |           |              |
|  |  | A/proenkephalin/PENK                            | 131330 | NM_006211 | 8q23-q24     |
|  |  | Opioid Receptor, Mu-1; Oprm1                    | 600018 | NM_000914 | 6q24-q25     |
|  |  | Opioid Receptor, Kappa-1; Oprk1                 | 165196 | U17298    | 8q11.2       |



|                                  |                     |                                                       |        |           |              |
|----------------------------------|---------------------|-------------------------------------------------------|--------|-----------|--------------|
|                                  | <b>Receptors</b>    | opioid receptor-like 1/OPRL 1                         | 602548 | X77130    | *****        |
|                                  |                     | Opioid Receptor, Delta-1; Oprd1                       | 165195 | U10504    | 1p36.1-p34.3 |
|                                  |                     | Opioid Receptor, Sigma 1                              | 601978 | U75283    | *****        |
|                                  |                     | opioid binding cell adhesion molecule/OBCAM           | 600632 | *****     | Chr.11       |
|                                  |                     | G protein-coupled receptor 7/GPR7                     | 600730 | U22491    | 0q11.2-q21.1 |
| <b>Oxytocin</b>                  | <b>Biosynthesis</b> | G protein-coupled receptor 8/GPR8                     | 600731 | U22492    | 20q13.3      |
|                                  |                     | Oxytocin                                              | 167050 | M25650    | 20p13        |
|                                  |                     | Oxytocin receptor                                     | 167055 | X64878    | 3p26.2       |
|                                  |                     | Leucyl/cystinyl aminopeptidase                        | 151300 | U62768    | *****        |
|                                  |                     | Cholecystokinin/CCK                                   | 118440 | L00354    | 3pter-p21    |
| <b>Cholecystokinin (CCK)</b>     | <b>Biosynthesis</b> | Cholecystokinin A receptor/CCKAR                      | 118444 | L13605    | 4p15.2-p15.1 |
|                                  |                     | Cholecystokinin B receptor/CCKBR                      | 118445 | L08112    | 1p15.5-p15.4 |
|                                  |                     | Neuropeptide Y/NPY                                    | 162640 | K01911    | 7p15.1       |
|                                  |                     | Neuropeptide Y receptor Y1/NPY1R                      | 162641 | M84755    | 4q31.3-q32   |
|                                  |                     | Neuropeptide Y receptor Y2/NPY2R                      | 162642 | U32500    | 4q31         |
| <b>Neuropeptide Y (NPY)</b>      | <b>Receptors</b>    | Neuropeptide Y receptor Y3/chemokine receptor 4/CXCR4 | 162643 | X71635    | 2q21         |
|                                  |                     | Neuropeptide Y receptor Y5                            | 602001 | U94320    | 4q31-q32     |
|                                  |                     | Neuropeptide Y receptor Y6                            | 601770 | D86519    | 5q31         |
|                                  |                     | leptin/LEP                                            | 164160 | NM_000230 | 7q31.3       |
|                                  |                     | leptin receptor/LEPR                                  | 601007 | NM_002303 | 1p31         |
| <b>Leptin</b>                    | <b>Biosynthesis</b> | Neurotensin                                           | 162650 | U91618    | 12q21        |
|                                  |                     | prolyl endopeptidase/PREP                             | 600400 | NM_002726 | 6q22         |
|                                  |                     | Neurotensin receptor                                  | 162651 | X70070    | 20q13        |
|                                  |                     | Neurokinin A/Tachykinin 1 or 2/Substance P or K       | 162320 | U37529    | 7q21-q22     |
|                                  |                     | Neurokinin B/Tachykinin 3                             | 162330 | *****     | 12q13-q21    |
| <b>Neurotensin Pathway</b>       | <b>Receptors</b>    |                                                       |        |           |              |
|                                  |                     |                                                       |        |           |              |
|                                  |                     |                                                       |        |           |              |
|                                  |                     |                                                       |        |           |              |
|                                  |                     |                                                       |        |           |              |
| <b>Tachykinin or Substance P</b> | <b>Biosynthesis</b> |                                                       |        |           |              |
|                                  |                     |                                                       |        |           |              |
|                                  |                     |                                                       |        |           |              |
|                                  |                     |                                                       |        |           |              |
|                                  |                     |                                                       |        |           |              |

|                       |              |                                                                                       |        |           |              |
|-----------------------|--------------|---------------------------------------------------------------------------------------|--------|-----------|--------------|
| Neurokinin<br>Pathway | Receptors    | Tachykinin NK1 receptor/TACR1                                                         | 162323 | M81797    | Chr.2        |
|                       |              | Tachykinin NK2 receptor/TACR2                                                         | 162321 | M57414    | 10q11-q21    |
|                       |              | Tachykinin NK3 receptor/TACR3                                                         | 162332 | M89473    | *****        |
|                       | Biosynthesis | kininogen/KNG                                                                         | 228960 | *****     | 3q27         |
| Bradykinin            |              | kallikrein 1/KLK1                                                                     | 147910 | AH002853  | 9q13.2-q13.4 |
|                       | Receptor     | bradykinin receptor B1/BDKRB1 G<br>protein-coupled                                    | 600337 | NM_000710 | 4q32.1-q32.2 |
|                       |              | bradykinin receptor B2/BDKRB2 G<br>protein-coupled                                    | 113503 | NM_000623 | 4q32.1-q32.2 |
|                       |              | angiotensinogen                                                                       | 106150 | NM_000029 | 1q42-q43     |
| Angiotensin           | Biosynthesis | renin/REN                                                                             | 179820 | NM_000537 | 1q32         |
|                       |              | renin-binding protein/RENBP                                                           | 312420 | D10711    | Xq28         |
|                       |              | angiotensin converting<br>enzyme/dipeptidyl carboxypeptidase                          | 106180 | NM_000789 | 17q23        |
|                       | Receptors    | angiotensin receptor 1/AGTR1A                                                         | 106165 | M87290    | 3q21-q25     |
| Vasopressin           |              | angiotensin II receptor type 2/AGTR2                                                  | 300034 | U10273    | Xq22-q23     |
|                       |              | vascular angiotensin II receptor type<br>1B/AGTR1B                                    | 600015 | NM_004835 | *****        |
|                       | Catabolism   | prolylcarboxypeptidase/PRCP                                                           | 176785 | NM_005040 | 11q14        |
|                       | Biosynthesis | Arginine Vasopressin                                                                  | 192340 | X03172    | 20p13        |
| Vasopressin           | Receptors    | Arginine Vasopressin Receptor<br>1A/AVPR1A                                            | 600821 | AF030625  | 12q14-q15    |
|                       |              | Arginine Vasopressin Receptor<br>1B/AVPR1B                                            | 600264 | AF030512  | 1q32         |
|                       |              | Arginine vasopressin receptor 2                                                       | 304800 | AF030626  | Xq28         |
|                       | Catabolism   | Leucyl/cystinyl aminopeptidase                                                        | 151300 | U62768    | *****        |
| Biosynthesis          |              | prepro-vasoactive intestinal<br>adenylate-cyclase activating<br>polypeptide 1/ADCYAP1 | 192320 | AH003029  | 6q26-q27     |
|                       |              |                                                                                       | 102980 | NM_001117 | 18p11        |

|                            |                                      |                     |                                                               |        |           |              |
|----------------------------|--------------------------------------|---------------------|---------------------------------------------------------------|--------|-----------|--------------|
| <b>Peptide Hormones</b>    | <b>Vasoactive Intestinal Peptide</b> | <b>Receptor</b>     | vasoactive intestinal peptide receptor 1/VIPR1                | 192321 | *****     | 3p22         |
|                            |                                      |                     | vasoactive intestinal peptide receptor 2/VIPR2                | 601970 | L40764    | 7q36.3       |
|                            |                                      |                     | adenylate-cyclase activating polypeptide 1 receptor/ADCYAP1R1 | 102981 | D17516    | 7p14         |
| <b>Calcitonin and CGRP</b> | <b>Biosynthesis</b>                  |                     | calcitonin/calcitonin gene-related peptide                    | 114130 | M12667    | 1p15.2-p15.1 |
|                            |                                      |                     | calcitonin/calcitonin gene-related peptide                    | 114160 | X02404    | 1p15.2-p15.2 |
|                            |                                      | <b>Receptor</b>     | calcitonin receptor/CALCR                                     | 114131 | L00587    | 7q21.3       |
| <b>CRH</b>                 | <b>Biosynthesis</b>                  |                     | calcitonin receptor-like/CALCRL                               | 114190 | NM_005795 | *****        |
|                            |                                      |                     | Corticotropin releasing hormone/CRH                           | 122560 | NM_000756 | 8q13         |
|                            |                                      |                     | urocortin/UCN                                                 | 600945 | NM_003353 | Chr.2        |
|                            | <b>Receptors</b>                     |                     | urocortin 2/UCN2                                              | 604097 | AF104118  | *****        |
|                            |                                      |                     | Corticotropin releasing hormone receptor 1                    | 122561 | U16273    | 17q12-q22    |
|                            |                                      |                     | Corticotropin releasing hormone receptor 2                    | 602034 | NM_001883 | 7p21-p15     |
| <b>TRH</b>                 | <b>Biosynthesis</b>                  |                     | Corticotropin releasing hormone-binding protein               | 122559 | X58022    | 5q11.2-q13.3 |
|                            | <b>Receptors</b>                     |                     | thyrotropin releasing hormone/TRH                             | 275120 | AH001523  | 3p           |
| <b>TSH</b>                 | <b>Biosynthesis</b>                  |                     | thyrotropin releasing hormone receptor/G protein coupled/TRHR | 188545 | X75071    | 8q23         |
|                            |                                      |                     | chorionic gonadotropin alpha chain/TSHA/CGA                   | 118850 | NM_000735 | 6q21.1-q23   |
|                            | <b>Receptor</b>                      |                     | thyroid stimulating hormone beta                              | 188540 | AH001548  | 1p13         |
|                            |                                      |                     | thyroid stimulating hormone receptor                          | 603372 | NM_000369 | 14q31        |
|                            |                                      | <b>Biosynthesis</b> | gonadotropin releasing hormone 1/LHRH/GNRH1                   | 152760 | NM_000825 | 8p21-p11.2   |

| GRH          | Biosynthesis | gonadotropin releasing hormone<br>2/LHRH/GNRH2                                                      | 602352 | NM_001501 | 20p13      |
|--------------|--------------|-----------------------------------------------------------------------------------------------------|--------|-----------|------------|
|              |              | gonadotropin releasing hormone<br>receptor/G protein-<br>coupled/LHRH/GNRHR                         | 138850 | NM_000406 | 4q21.2     |
| FSH          | Receptor     | gonadotropin releasing hormone-<br>coupled/LHRH/GNRHR                                               | 136530 | AH002701  | 11p13      |
|              |              | follicle stimulating hormone-<br>inhibin, beta A (activin A, activin AB<br>alpha polypeptide)/INHBA | 147290 | NM_002192 | 7p15-p13   |
|              |              | activin A receptor, type I/ACVR1                                                                    | 102576 | NM_001105 | 2q23-q24   |
|              |              | activin A receptor, type IB/ACVR1B                                                                  | 601300 | NM_004302 | 12q13      |
|              |              | activin A receptor type II-like<br>1/ACVRL1                                                         | 601284 | NM_000020 | 12q11-q14  |
|              |              | activin typeII A receptor/ACVR2                                                                     | 102581 | D31770    | *****      |
|              |              | activin A receptor, type IIB/ACVR2B                                                                 | 602730 | NM_001106 | 3p22-p21.3 |
|              |              | alpha-inhibin/INHA                                                                                  | 147380 | M13144    | 2q33-q36   |
|              |              | beta-B inhibin/beta C inhibin//INHBC                                                                | 601233 | M13437    | 12q13.1    |
|              |              | follicle stimulating hormone<br>receptor/FSHR                                                       | 136435 | NM_000145 | 2p21-p16   |
| Somatostatin | Receptor     | FSH primary response (LRPR1, rat)<br>homolog 1/FSHPRH1                                              | 300065 | NM_006733 | Xq22       |
|              |              | Somatostatin                                                                                        | 182450 | J00306    | 3q28       |
|              |              | preprocartistatin                                                                                   | 602784 | NM_001302 | 1p36       |
|              |              | Somatostatin receptor 1/G protein-<br>coupled                                                       | 182451 | M81829    | 14q13      |
|              |              | Somatostatin receptor 2                                                                             | 182452 | M81830    | 17q24      |
|              |              | Somatostatin receptor 3/adenyl cyclase<br>coupled                                                   | 182453 | M96738    | 22q13.1    |
|              |              | Somatostatin receptor 4                                                                             | 182454 | L07833    | 20p11.2    |
|              |              | Somatostatin receptor 5                                                                             | 182455 | D16827    | 16p13.3    |
|              | Biosynthesis |                                                                                                     |        |           |            |
|              |              |                                                                                                     |        |           |            |
|              | Receptors    |                                                                                                     |        |           |            |
|              |              |                                                                                                     |        |           |            |

|                         |                     |                                                                   |        |           |              |
|-------------------------|---------------------|-------------------------------------------------------------------|--------|-----------|--------------|
| <b>GHRH</b>             | <b>Biosynthesis</b> | growth hormone releasing hormone/GHRH                             | 139190 | AH002712  | 20q11.2      |
|                         | <b>Receptor</b>     | growth hormone releasing hormone receptor/G protein-coupled/GHRHR | 139191 | U34195    | 7p15-p14     |
| <b>Growth Hormone</b>   | <b>Biosynthesis</b> | growth hormone 1/somatotropin/GH1                                 | 139250 | NM_000515 | 17q22-q24    |
|                         | <b>Receptor</b>     | growth hormone receptor/GHR                                       | 600946 | NM_000163 | 5p13-p12     |
| <b>ACTH</b>             | <b>Biosynthesis</b> | proopiomelanocortin                                               | 176830 | NM_000939 | 2p23.3       |
|                         | <b>Receptor</b>     | melanocortin 2 receptor/ACTH receptor/MC2R                        | 202200 | NM_000529 | 18p11.2      |
| <b>Prolactin</b>        | <b>Biosynthesis</b> | prolactin/PRL                                                     | 176760 | NM_000948 | 6p22.2-p21.3 |
|                         | <b>Receptor</b>     | prolactin receptor/PRLR                                           | 176761 | NM_000949 | 5p13-p12     |
| <b>Galanin</b>          | <b>Biosynthesis</b> | preprogalanin/GAL1                                                | 137035 | L11144    | 1q13.3-q13.5 |
|                         | <b>Receptor</b>     | galanin receptor 1 (brain)/GALR1                                  | 600377 | NM_001480 | 18q23        |
|                         | <b>Receptor</b>     | galanin receptor 2/GALR2                                          | 603691 | NM_003857 | 17q25.3      |
|                         |                     | galanin receptor 3 (brain)/GALR3                                  | 603692 | NM_003614 | 2q12.2-q13.1 |
| <b>Bombesin</b>         | <b>Biosynthesis</b> | gastrin-releasing polypeptide/bombesin/GRP                        | 137260 | NM_002091 | 18q21        |
|                         |                     | neuromedin B/NMB                                                  | 162340 | M21551    | 15q22-qter   |
|                         | <b>Receptor</b>     | gastrin-releasing polypeptide receptor/G protein-coupled/GRPR     | 305670 | D87058    | Xp22.3-p21.2 |
|                         |                     | neuromedin B receptor/g protein-coupled/NMBR                      | 162341 | *****     | 6q21-qter    |
| <b>Glucagon Pathway</b> |                     | bombesin-like receptor 3/BRS3                                     | 300107 | NM_001727 | Xq26-q28     |
|                         | <b>Biosynthesis</b> | preproglucagon/GCG                                                | 138030 | X03991    | 2q36-q37     |
|                         | <b>Receptor</b>     | glucagon receptor/GCGR                                            | 138033 | NM_000160 | 17q25        |
|                         |                     | glucagon-like peptide 1                                           | 138032 | U01156    | 6p21         |
|                         |                     | glucagon-like peptide 2                                           | 603659 | *****     | 17p13.3      |
|                         |                     | carbamoyl synthase (6.3.2.11)                                     | *****  | *****     | *****        |

| Carnosine Pathway      | Biosynthesis                         | homocarnosine synthase                                                           | *****                       | *****     | *****     |
|------------------------|--------------------------------------|----------------------------------------------------------------------------------|-----------------------------|-----------|-----------|
|                        | Receptor                             | carnosine receptor                                                               | *****                       | *****     | *****     |
| Steroid Hormones       | Catabolism                           | carnosinase/Xaa-his dipeptidase (3.4.13.3)                                       | *****                       | *****     | *****     |
|                        | Biosynthesis                         | cytochrome P450, subfamily XIX (androgen aromatase)/CYP19                        | 107910                      | NM_000103 | 15q21.1   |
|                        | Receptors                            | estrogen receptor 1 (ESR1)                                                       | 133430                      | M12674    | 6q25.1    |
|                        |                                      | estrogen receptor 2 (ESR2)                                                       | 601663                      | X99101    | 14q       |
|                        |                                      | estrogen-related receptor                                                        | 601998                      | NM_004451 | 11q12     |
| Catabolism             | estrogen-related receptor beta/ESRRB | 602167                                                                           | NM_004452                   | 14q24.3   |           |
| Testosterone /DHT      | Catabolism                           | estrogen-preferring                                                              | 600043                      | NM_005420 | 4q13.1    |
|                        | Biosynthesis                         | steroid 5-alpha-reductase 1/SRD5A1                                               | 184753                      | AH003000  | 5p15      |
|                        |                                      | steroid 5-alpha-reductase 2/SRD5A2                                               | 264600                      | NM_000348 | 2p23      |
|                        |                                      | aldo-keto reductase family 1, member C4/3-a hydroxysteroid dehydrogenase/AKR1C4  | 600451                      | *****     | 10p15-p14 |
|                        | Receptors                            | androgen receptor                                                                | 313700                      | M20132    | Xq11-q12  |
| Glucocorticoid steroid | Catabolism                           | UDP glycosyltransferase 2 family, polypeptide B17/UGT2B17                        | 601903                      | NM_001077 | 4q13      |
|                        | Biosynthesis                         | cytochrome P450, subfamily XXI (steroid 21-a-hydroxylase)/CYP21                  | 201910                      | M13936    | 6p21.3    |
|                        |                                      | cytochrome P450, subfamily XIB, polypeptide 2 (steroid 11-b-hydroxylase)/CYP11B2 | 124080                      | NM_000498 | 8q21      |
|                        |                                      | Receptors                                                                        | glucocorticoid receptor/GRL | 138040    | NM_000176 |
|                        | Metabolism                           | corticosteroid binding globulin precursor/CBG                                    | 122500                      | NM_001756 | 14q32.1   |
|                        |                                      | hydroxy-D-5-steroid dehydrogenase, 3 b- and steroid D-isomerase 2/HSD3B2         | 201810                      | NM_000198 | 1p13.1    |

|                         |                                                                      |        |           |           |
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| <b>Calcium Channels</b> | voltage-dependent calcium channel, P/Q type, alpha 1A                | 601011 | NM_000068 | 19p13     |
|                         | calcium channel, voltage-dependent, L type, alpha 1B subunit/CACNA1B | 601012 | NM_000718 | 9q34      |
|                         | calcium channel, voltage-dependent, L type, alpha 1C subunit/CACNA1C | 114205 | NM_000719 | 12p13.3   |
|                         | calcium channel, voltage-dependent, L type, alpha 1D subunit/CACNA1D | 114206 | NM_000720 | 3p14.3    |
|                         | L-type voltage dependent calcium channel alpha 1S subunit/CACNA1S    | 114208 | NM_000069 | 1q32      |
|                         | calcium channel, voltage-dependent, beta 1 subunit/CACNB1            | 114207 | NM_000723 | 17q21-q22 |
|                         | voltage dependent calcium channel beta 2 subunit/CACNB2              | 600003 | U07139    | 10p12     |
|                         | voltage dependent calcium channel beta 3 subunit/CACNB3              | 601958 | NM_000725 | 12q13     |
|                         | voltage dependent calcium channel beta 4 subunit/CACNB4              | 601949 | *****     | 2q22-q23  |
|                         | calcium channel, voltage-dependent, alpha 2/delta subunit/CACNA2D1   | 114204 | Z28613    | 7q21-q22  |
|                         | calcium channel, voltage-dependent, gamma subunit/CACNG              | 114209 | NM_000727 | 17q24     |
|                         | neuronal voltage dependent calcium channel gamma subunit/CACNG2      | 602911 | NM_006078 | *****     |
|                         | ATPase, Ca++ transporting, plasma membrane 1/ATP2B1                  | 108731 | NM_001682 | 12q21-q23 |
|                         | ATPase, Ca++ transporting, plasma membrane 2/ATP2B2                  | 108733 | NM_001683 | 3p26-p25  |
|                         | ATPase, Ca++ transporting, plasma membrane 3/ATP2B3                  | 300014 | AF060497  | Xq28      |

|                                                                 |        |           |              |
|-----------------------------------------------------------------|--------|-----------|--------------|
| ATPase, Ca++ transporting, plasma membrane 4/ATP2B4             | 108732 | NM_001684 | 1q25-q32     |
|                                                                 | 180901 | AH006668  | 19q13.1      |
| gene/RYR1                                                       | 170500 | U24693    | 7q23.1-q25.3 |
| sodium channel alpha-subunit/SCN4A                              | 182390 | M94055    | 2q23-q24.3   |
| type II voltage dependent sodium channel alpha 1 subunit/SCN2A1 | 603415 | NM_002977 | 2q24         |
| type IX voltage dependent sodium channel alpha subunit/SCN9A    | 182389 | S71446    | 2q24         |
| type I voltage dependent sodium channel alpha subunit/SCN1A     | 182391 | S69887    | 2q24         |
| type III voltage dependent sodium channel alpha subunit/SCN3A   | 601327 | NM_004588 | 11q22-qter   |
| type II voltage dependent sodium channel beta subunit/SCN2B     | 182392 | M55662    | 2q21-q23     |
| type VI voltage dependent sodium channel alpha subunit/SCN6A    | 603967 | NM_000334 | 7q23.1-q25.3 |
| type IV voltage dependent sodium channel alpha subunit/SCN4A    | 600163 | NM_000335 | 3p24-p21     |
| type V voltage dependent sodium channel alpha subunit/SCN5A     | 600702 | *****     | 12q13        |
| type VIII voltage dependent sodium channel alpha subunit/SCN8A  | 601219 | M55662    | 2q23-q24     |
| type II voltage dependent sodium channel alpha 2 subunit/SCN2A2 | 600235 | NM_001037 | 19q13.1      |
| type I voltage dependent sodium channel beta subunit/SCN1B      | 601784 | NM_001094 | 17q11.2-q12  |
| voltage independent neuronal sodium channel 1/ACCN1             |        |           |              |

### Sodium Channels

### Channels



|                    |                                                                           |        |           |          |
|--------------------|---------------------------------------------------------------------------|--------|-----------|----------|
| Potassium Channels | voltage independent neuronal sodium channel 2/ACCN2                       | 602866 | NM_001095 | 12q12    |
|                    | cyclic nucleotide gated hyperpolarization activated potassium             | 602780 | AF064876  | *****    |
|                    | cyclic nucleotide gated hyperpolarization activated potassium             | 602781 | AF064877  | *****    |
|                    | voltage dependent potassium channel, KQT-like subfamily, member           | 602235 | NM_000218 | 20q13.3  |
|                    | voltage dependent potassium channel, KQT-like subfamily, member           | 602232 | AF033347  | 8q24     |
|                    | voltage dependent potassium channel, subfamily F, member 1/KCNF1          | 603787 | NM_002236 | 2p25     |
|                    | voltage dependent potassium channel, subfamily H, member 1/KCNH2          | 603305 | NM_002238 | 1q32-q41 |
|                    | inwardly rectifying potassium channel, subfamily J, member 4/KCNJ4        | 600504 | NM_004981 | 22q13.1  |
|                    | inwardly rectifying potassium channel, subfamily J, member 14/KCNJ14      | 603953 | *****     | *****    |
|                    | inwardly rectifying potassium channel, subfamily J, member 2/KCNJ3/HHIRK1 | 600681 | NM_000891 | *****    |
|                    | inwardly rectifying potassium channel, subfamily J, member 10/KCNJ10      | 602208 | *****     | 1q       |
|                    | potassium channel, subfamily J, member 13/KCNJ13                          | 603208 | AJ007557  | 2q37     |
|                    | voltage dependent potassium channel, subfamily K, member 1/KCNK1          | 601745 | NM_002245 | 1q42-q43 |
|                    | voltage dependent potassium channel, subfamily K, member 2/KCNK2          | 603219 | *****     | 1q41     |

|          |                                                                  |        |           |             |
|----------|------------------------------------------------------------------|--------|-----------|-------------|
|          | voltage dependent potassium channel, subfamily K, member 3/KCNK3 | 603220 | NM_002246 | 2p23        |
|          | G protein coupled potassium channel, subfamily J, member         | 601534 | NM_002239 | 2q24.1      |
|          | G protein coupled potassium channel inward rectifier/GIRK3       | 600932 | *****     | 1q21-q23    |
|          | voltage dependent potassium channel, subfamily S, member 1/KCNS1 | 602905 | *****     | *****       |
|          | voltage dependent potassium channel, subfamily S, member 2/KCNS2 | 602906 | *****     | 8q22        |
|          | voltage dependent potassium channel, subfamily S, member 3/KCNK3 | 603888 | AF043472  | 2p24        |
|          | large conductance Ca-activated K channel M type subunit 1B       | 603951 | NM_004137 | 5q34        |
|          | large conductance Ca-activated K channel M type subunit 1A       | 600150 | U09384    | Chr.10      |
|          | chloride channel, calcium activated, family member 1/CLCA1       | 603906 | NM_001285 | 1p31-p22    |
|          | chloride channel, calcium activated, family member 2/CLCA2       | 604003 | NM_006536 | *****       |
| Chloride | chloride channel 1, skeletal muscle/CLCN1                        | 118425 | NM_000083 | 7q35        |
|          | chloride channel 2/CLCN2                                         | 600570 | NM_004366 | 3q26-qter   |
|          | chloride channel 3/CLCN3                                         | 600580 | NM_001829 | 4q33        |
|          | chloride channel 4/CLCN4                                         | 302910 | NM_001830 | Xp22.3      |
|          | chloride channel 5/CLCN5                                         | 300008 | NM_000084 | Xp11.22     |
|          | chloride channel 6/CLCN6                                         | 602726 | NM_001286 | 1p36        |
|          | phospholipase A2 group                                           | 172411 | NM_000300 | 1p35        |
|          | phospholipase A2 group IB/PLA2G1B                                | 172410 | NM_000928 | 12q23-q24.1 |

|                       |                     |                                                       |        |           |              |
|-----------------------|---------------------|-------------------------------------------------------|--------|-----------|--------------|
| <b>Prostaglandins</b> | <b>Biosynthesis</b> | phospholipase A2 group X/PLA2G10                      | 603603 | *****     | 16p13.1-p12  |
|                       |                     | phospholipase A2 group IV A/PLA2G4A                   | 600522 | U08374    | 1q25         |
|                       |                     | phospholipase A2 group VI/PLA2G6                      | 603604 | AF064594  | 22q13.1      |
|                       |                     | phospholipase A2 group IVC/PLA2G4C                    | 603602 | *****     | chr. 19      |
|                       |                     | phospholipase A2 group V/PLA2G5                       | 601192 | NM_000929 | 1p36-p34     |
|                       |                     | phospholipase C beta 3                                | 600230 | U26425    | 11q13        |
|                       |                     | lysosomal acid lipase                                 | 278000 | NM_000235 | 10q24-q25    |
|                       |                     | prostaglandin endoperoxide synthetase 1/COX1/PTGS1    | 176805 | AH001520  | 9q32-q33.3   |
|                       |                     | prostaglandin endoperoxide synthetase 2/COX2/PTGS2    | 600262 | NM_000963 | 1q25.2-q25.3 |
|                       |                     | thromboxane A synthase 1/TBXAS1                       | 274180 | EG_D34613 | 7q34         |
|                       |                     | prostaglandin D2 synthase                             | 602598 | M61900    | *****        |
|                       |                     | prostaglandin I2 synthase/prostacyclin synthase/PTGIS | 601699 | EG_D83393 | 20q13        |
|                       | <b>Receptors</b>    | prostaglandin E receptor 1, EP1 subtype/PTGER1        | 176802 | NM_000955 | 19p13.1      |
|                       |                     | prostaglandin E receptor 2, EP2 subtype/PTGER2        | 176804 | *****     | 5p13.1       |
|                       |                     | prostaglandin E receptor 3, EP3 subtype/PTGER3        | 176806 | NM_000957 | 1p31.2       |
|                       |                     | prostaglandin E receptor 4, EP4 subtype/PTGER4        | 601586 | NM_000958 | 5p13.1       |
|                       |                     | prostaglandin F receptor/PTGFR                        | 600563 | L24470    | 1p31.1       |
|                       |                     | prostaglandin F2 receptor negative regulator/PTGFRN   | 601204 | U26664    | 1p13.1-q21.3 |
|                       |                     | prostaglandin I2 receptor/PTGIR/prostacyclin receptor | 600022 | SEG_HUMH  | 19q13.3      |

|  |  |                                                          |                                           |                     |                                                               |        |           |             |
|--|--|----------------------------------------------------------|-------------------------------------------|---------------------|---------------------------------------------------------------|--------|-----------|-------------|
|  |  | <b>Inflammation<br/>(additional genes in Immunology)</b> | <b>Platelet<br/>Activating<br/>Factor</b> | <b>Catabolism</b>   | 15-hydroxyprostaglandin dehydrogenase/HPGD                    | 601688 | NM_000860 | 4q34-q35    |
|  |  |                                                          |                                           |                     | aldo-keto reductase family 1, member C2/AKR1C2                | 600450 | NM_001353 | 10p15-p14   |
|  |  |                                                          |                                           | <b>Biosynthesis</b> | CDP-choline:alkylacetylgllycerol cholinephosphotransferase    | *****  | *****     | *****       |
|  |  |                                                          |                                           |                     | phospholipase A2 group                                        | 172411 | NM_000300 | 1p35        |
|  |  |                                                          |                                           |                     | phospholipase A2 group IB/PLA2G1B                             | 172410 | NM_000928 | 12q23-q24.1 |
|  |  |                                                          |                                           |                     | phospholipase A2 group X/PLA2G10                              | 603603 | *****     | 16p13.1-p12 |
|  |  |                                                          |                                           |                     | phospholipase A2 group IVA/PLA2G4A                            | 600522 | U08374    | 1q25        |
|  |  |                                                          |                                           |                     | phospholipase A2 group VI/PLA2G6                              | 603604 | AF064594  | 22q13.1     |
|  |  |                                                          |                                           |                     | phospholipase A2 group IVC/PLA2G4C                            | 603602 | *****     | chr. 19     |
|  |  |                                                          |                                           |                     | phospholipase A2 group V/PLA2G5                               | 601192 | NM_000929 | 1p36-p34    |
|  |  |                                                          |                                           |                     | platelet activating factor receptor/PTAFR                     | 173393 | M88177    | 1p35-p34.3  |
|  |  |                                                          |                                           |                     | platelet activating factor acetylhydrolase 1/PAFAH1           | 601690 | NM_005084 | 6p21.2-p12  |
|  |  |                                                          |                                           | <b>Catabolism</b>   | platelet activating factor acetylhydrolase, isoform 1B, alpha | 601545 | NM_000430 | 17p13.3     |
|  |  |                                                          |                                           |                     | platelet activating factor acetylhydrolase, isoform 1B, beta  | 602508 | NM_002572 | 11q23       |
|  |  |                                                          |                                           |                     | platelet activating factor acetylhydrolase, isoform 1B, gamma | 603074 | NM_002573 | 19q13.1     |
|  |  |                                                          |                                           |                     | platelet activating factor acetylhydrolase 2/PAFAH2           | 602344 | NM_000437 | *****       |
|  |  |                                                          |                                           |                     | interferon alpha1 (IFNa1)                                     | 147660 | X02956    | 9p22        |
|  |  |                                                          |                                           |                     | interferon alpha2 (IFNa2)                                     | 147562 | *****     | 9p22        |

|                     |                                                                  |        |           |               |
|---------------------|------------------------------------------------------------------|--------|-----------|---------------|
| <b>Interferon</b>   | interferon beta1 (IFNb1)                                         | 147640 | V00546    | 9p21          |
|                     | interferon beta3 (IFNb3)                                         | 147860 | *****     | Chr.8         |
|                     | interferon omegal (IFNw1)                                        | 147553 | X02669    | 9p21          |
|                     | interferon gamma (IFNg)                                          | 147570 | L07633    | 12q14         |
|                     | interferon alpha receptor 1 (IFNAR1)                             | 107450 | X77722    | 21q22.1       |
|                     | interferon alpha receptor 2 (IFNAR2)                             | 147569 | U68755    | 21q22.1-q22.2 |
|                     | interferon gamma receptor 1                                      | 107470 | J03143    | 6q23-q24      |
|                     | interferon gamma receptor 2                                      | 602376 | NM_000874 | 21q22.1       |
|                     | 2',5'-oligoadenylate synthetase                                  | 164350 | NM_006187 | 12q24.2       |
|                     | 2',5'-oligoadenylate synthetase                                  | 603350 | M87284    | 12q24.2       |
| <b>Interleukins</b> | 2',5'-oligoadenylate synthetase                                  | 603351 | *****     | 12q24.2       |
|                     | interleukin 1 alpha/IL1A                                         | 147760 | M15329    | 2q14          |
|                     | interleukin 1 beta/IL1B                                          | 147720 | K02770    | 2q14          |
|                     | interleukin 1 receptor, type 1/IL1R1                             | 147810 | M27492    | 2q12          |
|                     | interleukin 1 receptor, type 2/IL1R2                             | 147811 | NM_004633 | 2q12-q22      |
|                     | interleukin 8/IL8                                                | 146930 | M26383    | 4q12-q13      |
|                     | interleukin 8 receptor alpha/IL8R1                               | 146929 | M68932    | 2q35          |
|                     | interleukin 8 receptor beta/IL8R2                                | 146928 | M94582    | 2q35          |
|                     | interleukin 10/IL10                                              | 124092 | M57627    | 1q31-q32      |
|                     | interleukin 10 receptor alpha/IL101                              | 146933 | U00672    | 11q23.3       |
|                     | tumor necrosis factor alpha/TNFA                                 | 191160 | X01394    | 6p21.3        |
|                     | tumor necrosis factor                                            |        |           |               |
|                     | beta/TNFB/lymphotoxin alpha/LTA                                  | 153440 | NM_000595 | 6p21.3        |
|                     | tumor necrosis factor receptor                                   |        |           |               |
|                     | superfamily, member 1A/TNFRSF1A                                  | 191190 | NM_001065 | 12p13.2       |
| <b>MIF</b>          | tumor necrosis factor receptor                                   |        |           |               |
|                     | superfamily, member 1B/TNFRSF1B                                  | 191191 | NM_001066 | 1p36.3-p36.2  |
|                     | macrophage migration inhibitory factor (glycosylation-inhibiting | 153620 | NM_002415 | 22q11.2       |

## Cytokines

|                                                                             |          |             |                                                                                      |        |           |              |
|-----------------------------------------------------------------------------|----------|-------------|--------------------------------------------------------------------------------------|--------|-----------|--------------|
| Cardiovascular<br>or<br>(additional<br>genes in<br>Cardiovascular<br>or and | Clotting | Clotting    | factor I/fibrinogen a, alpha/FGA                                                     | 134820 | NM_000508 | 4q28         |
|                                                                             |          |             | factor I/fibrinogen b, beta/FGB                                                      | 134830 | AH003492  | 4q28         |
|                                                                             |          |             | factor I/fibrinogen g, gamma/FGG                                                     | 134850 | NM_000509 | 4q28         |
|                                                                             |          |             | factor II/prothrombin                                                                | 176930 | F2        | 11p11-q12    |
|                                                                             |          |             | factor III/thromboplastin                                                            | 134390 | NM_001993 | 1p22-p21     |
|                                                                             |          |             | factor V/proaccelerin/labile factor                                                  | 227400 | NM_000130 | 1q23         |
|                                                                             |          |             | factor VII/serum prothrombin<br>conversion accelerator                               | 227500 | NM_000131 | 13q34        |
|                                                                             |          |             | factor VIII/antihemophilic factor                                                    | 306700 | NM_000132 | Xq28         |
|                                                                             |          |             | factor IX/Christmas factor/plasma<br>thromboplastic component/hemophilia             | 306900 | NM_000133 | Xq27.1-q27.2 |
|                                                                             |          |             | factor X/Stuart factor                                                               | 227600 | NM_000504 | 13q34        |
|                                                                             |          |             | factor XI/plasma thromboplastin<br>antecedent                                        | 264900 | NM_000128 | 4q35         |
|                                                                             |          |             | factor XII/Hageman factor                                                            | 234000 | NM_000505 | 5q33-qter    |
|                                                                             |          |             | factor XIIIa1/fibrin-stabilizing factor                                              | 134570 | NM_000129 | 6p25-p24     |
|                                                                             |          |             | prekallikrein/Fletcher factor                                                        | 229000 | *****     | 4q35         |
|                                                                             |          |             | kininogen/Flaujeac factor                                                            | 228960 | *****     | 3q27         |
|                                                                             |          |             | solute carrier family 12, member<br>3/SLC12A3 (renal sodium/chloride<br>transporter) | 600968 | NM_000339 | 16q13        |
|                                                                             |          | Ion Pump    | renin/REN                                                                            | 179820 | NM_000537 | Xq28         |
|                                                                             |          |             | renin-binding protein/RENBP                                                          | 312420 | NM_002910 | 1q32         |
|                                                                             |          | Angiotensin | angiotensinogen/AGT                                                                  | 106150 | NM_000029 | 1q42-q43     |
|                                                                             |          |             | angiotensin II type 1 receptor/AGTR1                                                 | 106165 | M87290    | 3q21-q25     |
|                                                                             |          |             | guanine nucleotide binding protein (G<br>protein), beta polypeptide 3/GNB3           | 139130 | NM_002075 | 12p13        |

|              |                                |                                                                                |        |           |               |
|--------------|--------------------------------|--------------------------------------------------------------------------------|--------|-----------|---------------|
| <i>Renal</i> | <b>Hemostasis</b>              | dipeptidyl carboxypeptidase I<br>(angiotensin I converting<br>enzyme)/ACE/DCP1 | 106180 | NM_000789 | 17q23         |
|              |                                | atrial natriuretic peptide precursor<br>A/NPPA                                 | 108780 | X01471    | 1p36.2        |
|              | <b>Natriuretic<br/>Peptide</b> | atrial natriuretic peptide precursor<br>B/NPPB                                 | 600295 | *****     | 1p36.2        |
|              |                                | atrial natriuretic peptide precursor<br>C/NPPC                                 | 600296 | D28874    | 2q24-qter     |
|              |                                | natriuretic peptide receptor<br>A/ANPRA/NPR1                                   | 108960 | *****     | 1q21-q22      |
|              |                                | natriuretic peptide receptor<br>B/ANPRB/NPR2                                   | 108961 | *****     | 9p21-p12      |
|              |                                | natriuretic peptide receptor<br>C/ANPRC/NPR3                                   | 108962 | NM_000908 | 5p14-p12      |
|              |                                | endothelin 1/EDN1                                                              | 131240 | NM_001955 | 6p24-p23      |
|              |                                | endothelin 2/EDN2                                                              | 131241 | NM_001956 | 1p34          |
|              |                                | endothelin 3/EDN3                                                              | 131242 | NM_000114 | 20q13.2-q13.3 |
|              |                                | endothelin converting enzyme 1/ECE1                                            | 600423 | NM_001397 | 1p36.1        |
|              |                                | endothelin A receptor isoform delta<br>3/EDNRA                                 | 131243 | AF014826  | Chr. 4        |
|              | <b>Endothelin</b>              | endothelin receptor type B/EDNRB                                               | 131244 | NM_000115 | 13q22         |
|              |                                | cardiotrophin 1                                                                | 600435 | *****     | *****         |
|              |                                | leukemia inhibitory factor/LIF                                                 | 159540 | NM_002309 | 2q12.1-q12.2  |
|              |                                | ciliary neurotrophic factor/CNTF                                               | 118945 | NM_000614 | 11q12.2       |
|              |                                | nerve growth factor alpha                                                      | 162020 | *****     | *****         |
|              |                                | nerve growth factor beta                                                       | 162030 | NM_005378 | 1p13.1        |
|              |                                | nerve growth factor gamma                                                      |        |           |               |
|              |                                | subunit/NGFG                                                                   | 162040 | *****     | 19q13.3       |

**Growth  
Factor**

|                                       |        |           |              |
|---------------------------------------|--------|-----------|--------------|
| neurotrophin 3/NTF3                   | 162660 | NM_002527 | 12p13        |
| neurotrophin 5/NTF4/NTF5              | 162662 | NM_006179 | 19q13.3      |
| neurotrophin 6 alpha/NTF6A            | 604021 | NM_004149 | 19q13.3      |
| neurotrophin 6 beta/NTF6B             | 604022 | NM_004150 | chr. 19      |
| neurotrophin 6 gamma/NTF6G            | 604023 | NM_004151 | chr. 19      |
| brain derived neurotrophic            | 113505 | *****     | 11p13        |
| growth associated protein 43/GAP43    | 162060 | NM_002045 | Chr.3        |
| pleiotrophin/NEGF1/PTN                | 162095 | AH004121  | 7q33         |
| semaphorin 3A/SEMA3A                  | 603961 | *****     | *****        |
| glial growth factor 2/neuregulin      | 142445 | M94166    | 8p22-p11     |
| neuregulin 2/NRG2                     | 603818 | *****     | 5q23-q33     |
| neurite growth promoting factor       |        |           |              |
| 2/NEGF2                               | 162096 | *****     | 11p11.2      |
| glial cell derived neurotrophic       |        |           |              |
| factor/GDNF                           | 600837 | NM_000514 | 5p13.1-p12   |
| insulin-like growth factor            |        |           |              |
| 1/somatomedin C/IGF1                  | 147440 | M11568    | 12q22-q24.1  |
| insulin-like growth factor            |        |           |              |
| 2/somatomedin A/IGF2                  | 147470 | NM_000612 | 11p15.5      |
| transforming growth factor/TGFB1      | 190180 | M60315    | 9q13.1-q13.3 |
| transforming growth factor/TGFB2      | 190220 | M19154    | 1q41         |
| transforming growth factor/TGFB3      | 190230 | X14149    | 14q24        |
| ciliary neurotrophic factor           |        |           |              |
| receptor/CNTFR                        | 118946 | NM_001842 | 9p13         |
| nerve growth factor receptor/NGFR     | 162010 | NM_002507 | 17q21-q22    |
| neurotrophic tyrosine kinase receptor |        |           |              |
| type 1/NTRK1                          | 191315 | Y09033    | 1q21-q22     |
| neurotrophic tyrosine kinase receptor |        |           |              |
| type 2/NTRK2                          | 600456 | NM_006180 | 9q22.1       |



**Growth  
Factors and  
Receptors**

|                                                          |        |           |               |
|----------------------------------------------------------|--------|-----------|---------------|
| neurotrophic tyrosine kinase receptor<br>type 3/NTRK3    | 191316 | NM_002530 | 15q25         |
| reelin/RELN                                              | 600514 | NM_005045 | 7q22          |
| neuropilin 1/VEGF 165                                    | 602069 | NM_003873 | 10p12         |
| neuropilin 2/VEGF 165 receptor/NP2                       | 602070 | NM_003872 | 2q34          |
| homolog of Drosophila                                    | 603448 | AF071062  | 1p32-p31      |
| retinoic acid receptor alpha/RARA                        | 180240 | NM_000964 | 17q12         |
| retinoic acid receptor beta/RARB                         | 180220 | NM_000965 | 3p24          |
| retinoic acid receptor gamma/RARG                        | 180190 | M57707    | 12q13         |
| RAR related orphan receptor A/RORA                       | 600825 | NM_002943 | 15q21-q22     |
| RAR related orphan receptor B/RORB                       | 601972 | *****     | 9q22          |
| RAR related orphan receptor C/RORC                       | 602943 | NM_005060 | 1q21          |
| retinoid X receptor alpha/RXRA                           | 180245 | NM_002957 | 9q34.3        |
| retinoid X receptor beta/RXRB                            | 180246 | X66424    | 6p21.3        |
| retinoid X receptor gamma/RXRG                           | 180247 | U38480    | 1q22-q23      |
| vitamin B12 receptor/cubilin/CUBN                        | 602997 | NM_001081 | 10p12.1       |
| vitamin D receptor/VDR                                   | 601769 | NM_000376 | 12q12-q14     |
| cannabinoid receptor 1/G protein-<br>coupled/CNR1        | 114610 | NM_001840 | 6q14-q15      |
| oncogene ERBB3/HER3                                      | 190151 | NM_001982 | 12q13         |
| homolog 3 of Drosophila                                  | 600276 | NM_000435 | 19p13.2-p13.1 |
| Notch/NOTCH3                                             |        |           |               |
| SRC, FGR, YES-related oncogene                           | 137025 | NM_002037 | 6q21          |
| FYN/FYN (receptor tyrosine kinase)                       |        |           |               |
| receptor 1 for activated protein kinase<br>C/RACK1       | 176981 | *****     | *****         |
| insulin-like growth factor 1 receptor<br>precursor/IGF1R | 147370 | NM_000875 | 15q25-q26     |
| insulin-like growth factor 2<br>receptor/IGF2R           | 147280 | NM_000876 | 6q26          |

**Receptors**

|                                                                             |                                                                                  |        |           |              |
|-----------------------------------------------------------------------------|----------------------------------------------------------------------------------|--------|-----------|--------------|
| Growth and<br>Differentiation<br>on<br>(additional<br>genes in<br>Oncology) | TGF-B type I receptor/TGFR1                                                      | 190181 | AH006005  | 9q33-q34     |
|                                                                             | TGF-B type II receptor/TGFR2                                                     | 190182 | NM_003242 | 3p22         |
|                                                                             | TGF-B type III receptor/TGFR3                                                    | 600742 | L07594    | 1p33-p32     |
|                                                                             | fibroblast growth factor receptor<br>1/FGFR1                                     | 136350 | *****     | 8p11.2-p11.1 |
|                                                                             | fibroblast growth factor receptor<br>2/FGFR2                                     | 176943 | Y17131    | 10q26        |
|                                                                             | fibroblast growth factor receptor<br>3/FGFR3                                     | 134934 | NM_005247 | 4p16.3       |
|                                                                             | fibroblast growth factor receptor<br>4/FGFR4                                     | 134935 | NM_002011 | 5q35.1-qter  |
|                                                                             | laforin/EPM2A                                                                    | 254780 | AF084535  | 6q24         |
|                                                                             | steroid receptor coactivator 1/SRC1                                              | 602691 | NM_003743 | 2p23         |
|                                                                             | glucocorticoid receptor interacting<br>protein 1/GRIP1                           | 601993 | NM_006540 | *****        |
|                                                                             | nuclear receptor coactivator/AIB1                                                | 601937 | NM_006534 | 20q12        |
|                                                                             | p300/CBP associated factor/PCAF                                                  | 602303 | U57317    | 3p24         |
|                                                                             | CREB binding protein/CRB                                                         | 600140 | NM_004380 | 16p13.3      |
|                                                                             | cyclic AMP responsive element<br>binding protein 1/CREB1                         | 123810 | NM_004379 | 2q32.3-q34   |
|                                                                             | silencing mediator for retinoid and<br>thyroid hormone receptors/SMRT            | 600848 | NM_006312 | *****        |
|                                                                             | retinoic and thyroid hormone receptor<br>associated corepressor<br>1/TRAC1/NCOR1 | 600849 | NM_006311 | *****        |
|                                                                             | steroid receptor RNA activator/SRA                                               | 603819 | AF092038  | chr. 5       |
|                                                                             | protein kinase, cAMP-dependent<br>regulatory, type 1 beta/PRKAR1B                | 176911 | *****     | 7pter-p22    |
|                                                                             | early growth response 2/EGR2                                                     | 129010 | NM_000399 | 0q21.1-q22.1 |

|                                                          |        |           |              |
|----------------------------------------------------------|--------|-----------|--------------|
| neuronal growth-associated protein<br>SCG10/SCG10        | 600621 | *****     | *****        |
| apoptosis-related cysteine protease<br>2/caspase 2/CASP2 | 600639 | NM_006156 | 7q35         |
| apoptosis-related cysteine protease<br>1/caspase 1/CASPI | 147678 | L27475    | 1q22.2-q22.3 |
| neuronal apoptosis inhibitory<br>protein/NAIP            | 600355 | NM_004536 | 5q12.2-q13.3 |
| protein kinase C, alpha/PRKCA                            | 176960 | NM_002737 | 17q22-q23.2  |
| protein kinase C beta-II type/PRKCB1                     | 176970 | M13975    | 16p11.2      |
| protein kinase C, delta/PRKCD                            | 176977 | NM_006254 | 3p           |
| protein kinase C, epsilon/PRKCE                          | 176975 | NM_005400 | 2p21         |
| protein kinase C, gamma/PRKCG                            | 176980 | *****     | 19q13.4      |
| protein kinase C, iota/PRKCI                             | 300094 | NM_002740 | Xq21.3       |
| protein kinase C zeta/PRKCZ                              | 176982 | L14283    | *****        |
| protein kinase C-like 1/PRKCL1                           | 601032 | NM_002741 | 19p12        |
| protein kinase C-like 2/PRKCL2                           | 602549 | NM_006256 | *****        |
| inositol polyphosphate-1-<br>phosphatase/INPPI           | 147263 | NM_002194 | 2q32         |
| phosphodiesterase 1A, calmodulin-<br>dependent/PDE1A     | 171890 | NM_005019 | Chr.4        |
| phosphodiesterase 1B, calmodulin-<br>dependent/PDE1B     | 171891 | NM_000924 | 12q13        |
| phosphodiesterase 1C, calmodulin-<br>dependent/PDE1C     | 602987 | NM_005020 | *****        |
| phosphodiesterase 4A, cAMP-<br>specific/PDE4A            | 600126 | NM_006202 | 19p13.2      |
| phosphodiesterase 4B, cAMP-<br>specific/PDE4B            | 600127 | NM_002600 | 1p31         |

## Signaling

## Signaling

|               |               |                                                                            |        |           |              |
|---------------|---------------|----------------------------------------------------------------------------|--------|-----------|--------------|
|               |               | phosphodiesterase 4C, cAMP-specific/PDE4C                                  | 600128 | *****     | Chr.19       |
|               |               | phosphodiesterase 4D, cAMP-specific/PDE4D                                  | 600129 | NM_006203 | 5q12         |
|               |               | phosphodiesterase 7A, cAMP-specific/PDE7A                                  | 171885 | L12052    | 8q13-q22     |
|               |               | phosphodiesterase 8A, cAMP-specific/PDE8A                                  | 602972 | AF056490  | *****        |
|               |               | phosphodiesterase 9A, cAMP-specific/PDE9A                                  | 602973 | NM_002606 | 21q22.3      |
|               |               | telomerase protein component 1                                             | 601686 | U86136    | 14q11.2      |
|               |               | telomerase reverse transcriptase                                           | 187270 | AF015950  | 5p15.33      |
|               |               | telomerase RNA component                                                   | 602322 | U86046    | 3q21-q28     |
|               |               | superoxide dismutase 1/SOD1                                                | 147450 | NM_000454 | 21q22.1      |
|               |               | superoxide dismutase 2, mitochondrial/SOD2                                 | 147460 | X65965    | 6q25.3       |
|               |               | thioredoxin-dependent peroxide reductase/TDPXI                             | 600538 | NM_005809 | 13q12        |
|               |               | Peptide methionine sulfoxide reductase/MSRA                                | 601250 | *****     | *****        |
|               |               | lipoprotein, Lp(a)/LPA                                                     | 152200 | NM_005577 | 6q27         |
|               |               | succinate dehydrogenase complex, subunit C, integral membrane protein/SDHC | 602413 | NM_003001 | 1q21         |
|               |               | glucose-6-phosphate dehydrogenase/G6PD (mitochondrial)                     | 305900 | NM_000402 | Xq28         |
|               |               | aldehyde oxidase 1/AOX1                                                    | 602841 | NM_001159 | 2q33         |
|               |               | mitochondrial tRNA(lys)                                                    | 590060 | M37726    | mitochondria |
| Oxygen Stress | Oxygen Stress |                                                                            |        |           |              |

|                                   |                    |                                                                      |        |            |              |
|-----------------------------------|--------------------|----------------------------------------------------------------------|--------|------------|--------------|
| Mitochondrial Maintenance         | Translation        | mitochondrial tRNA(ser)(UCN)                                         | 59080  | S79597     | mitochondria |
|                                   |                    | mitochondrial tRNA(Gln)                                              | 556500 | S77916     | mitochondria |
|                                   |                    | mitochondrial tRNA(Thr)                                              | 556500 | S77921     | mitochondria |
| Electron Transport                | Protein Maturation | paraplegin (nuclear-encoded mitochondrial metalloprotease)           | 602783 | NM_003119  | 16q24.3      |
|                                   |                    | NADH-ubiquinone oxidoreductase flavoprotein 2, 24 kDa subunit/NDUFV2 | 600532 | EG_D885428 | p11.31-p11.3 |
|                                   |                    | cytochrome oxidase subunit I/MTCO1                                   | 516030 | AF035429   | mitochondria |
|                                   |                    | cystatin B/stefin B/CSTB                                             | 601145 | NM_000100  | 21q22.3      |
|                                   |                    | cystatin C/CST3                                                      | 105150 | NM_000099  | 20p11.2      |
|                                   |                    | ubiquitin carboxy-terminal esterase L1/UCHL1                         | 191342 | NM_004181  | 4p14         |
|                                   |                    | ubiquitin-protein ligase E3A/UBE3A                                   | 601623 | NM_000462  | 15q11-q13    |
|                                   |                    | peptidyl-prolyl isomerase A/cyclophilin A/PPIA                       | 123840 | Y00052     | 7p13         |
|                                   |                    | peptidyl-prolyl isomerase B/cyclophilin B/PPIB                       | 123841 | M60857     | chr. 15      |
|                                   |                    | peptidyl-prolyl isomerase C/cyclophilin C/PPIC                       | 123842 | S71018     | *****        |
| Protein Maturation and Catabolism |                    | peptidyl-prolyl isomerase D/cyclophilin D/PPID                       | 601753 | NM_005038  | 4q31.3       |
|                                   |                    | peptidyl-prolyl isomerase E/cyclophilin E/PPIE                       | *****  | NM_006112  | *****        |
|                                   |                    | FK506 binding protein 1A/immunophilin/FKBP1A                         | 186945 | NM_000801  | 20p13        |
|                                   |                    | FK506 binding protein 2/immunophilin/FKBP2                           | 186946 | NM_004470  | 1q13.1-q13.3 |
|                                   |                    |                                                                      |        |            |              |

|              |                                               |        |           |              |
|--------------|-----------------------------------------------|--------|-----------|--------------|
|              | FK506 binding protein 4/immunophilin/FKBP4    | 600611 | NM_002014 | *****        |
|              | FK506 binding protein 5/immunophilin/FKBP5    | 602623 | *****     | *****        |
|              | microsomal stress 70 protein ATPase core/STCH | 601100 | U04735    | 21q11.1      |
|              | heat shock protein, DNAJ-like 1/HSJ1          | 604139 | X63368    | 2q32-q34     |
|              | heat shock protein, DNAJ-like 2/HSJ2          | 602837 | NM_001539 | *****        |
|              | alpha-B-crystallin/CRYAB                      | 123590 | M28638    | 1q22.3-q23.1 |
|              | heat shock transcription factor 1/HSF1        | 140580 | NM_005526 | *****        |
|              | heat shock transcription factor 2/HSF2        | 140581 | NM_004506 | *****        |
|              | heat shock transcription factor 4/HSF4        | 602438 | NM_001538 | 16q21        |
|              | microtubule-associated protein tau/MAPT       | 157140 | NM_005910 | 17q21.1      |
| Cytoskeleton | tubulin, alpha, brain-specific/TUBA3          | 602529 | NM_006009 | 2q           |
|              | beta-tubulin gene/TUBB                        | 191130 | J00314    | 6p21.3       |
|              | tubulin, beta, 5/TUBB5                        | 602662 | NM_006087 | *****        |
|              | cadherin 2/NCAD/CDH2                          | 114020 | Z27440    | 18q11.2      |
| Adhesion     | calpain, large polypeptide L3/CAPN3           | 114240 | NM_000070 | 5q15.1-q21.1 |
|              | neural cell adhesion molecule                 | 308840 | X67912    | Xq28         |
|              | neural cell adhesion molecule                 | 116930 | *****     | 11q23.1      |
|              | neural cell adhesion molecule                 | 602040 | NM_004540 | 21q21        |
|              | neural cell adhesion                          | 601581 | U55258    | 7q31.1-q31.2 |
|              | opioid binding cell adhesion molecule/OBCAM   | 600632 | *****     | Chr.11       |
|              | nerve injury-induced protein 1/ninjurin/NINJ1 | 602062 | NM_004148 | 9q22         |
|              | protease inhibitor 12                         | 602445 | NM_005025 | *****        |

|                             |                                                                           |        |           |              |
|-----------------------------|---------------------------------------------------------------------------|--------|-----------|--------------|
| <b>Biosynthesis</b>         | cathepsin B/b-aCTSBmyloid precursor protein secretase/CTSB                | 116810 | M14221    | 8p22         |
|                             | thimet oligopeptidase 1/THOP1                                             | 601117 | NM_003249 | 19p13.3      |
|                             | amyloid beta A4 precursor                                                 | 104760 | NM_000484 | 1q21.3-q22.0 |
|                             | amyloid beta A4 precursor protein-like/APPL1                              | 104740 | *****     | 9q31-qter    |
|                             | presenilin 1/PSEN1 (membrane/adhesion)                                    | 104311 | NM_000021 | 14q24.3      |
| <b>Interacting Proteins</b> | presenilin 2/PSEN2 (membrane/adhesion)                                    | 600759 | NM_000447 | 1q31-q42     |
|                             | amyloid beta A4 precursor protein-binding, family A, member 1/APBA1/MINT1 | 602414 | NM_004664 | 9q13         |
|                             | amyloid beta A4 precursor protein-binding, family A, member 1/APBA2       | 602712 | *****     | 15q          |
|                             | amyloid beta A4 precursor protein-binding, family B, member 1/APBB1       | 602709 | NM_001164 | 11p15        |
|                             | amyloid beta A4 precursor protein-binding, family B, member 1/APBB2       | 602710 | U62325    | Chr.4        |
|                             | Munc 18-1 interacting protein                                             | 603452 | *****     | *****        |
|                             | apolipoprotein E/APOE                                                     | 107741 | NM_000041 | 19q13.2      |
|                             | c-jun                                                                     | 165160 | J04111    | 1p32-p31     |
|                             | low density lipoprotein receptor-related protein/LRP1                     | 107770 | NM_002332 | 2q13.1-q13.2 |
|                             | microtubule-associated protein tau/MAPT                                   | 157140 | NM_005910 | 17q21.1      |
|                             | synuclein alpha/SNCA                                                      | 163890 | NM_000345 | 4q21         |
|                             | synuclein beta/SNCB                                                       | 602569 | NM_003085 | 5q35         |
|                             | synuclein gamma/SNCG                                                      | 602998 | NM_003087 | 0q23.2-q23.3 |
| <b>β-amyloid Metabolism</b> |                                                                           |        |           |              |

|                           |  |                                                                       |        |           |              |
|---------------------------|--|-----------------------------------------------------------------------|--------|-----------|--------------|
| Cellular Maintenance      |  | hydroxyacyl-Coenzyme A dehydrogenase, type II/HADH2                   | 602057 | NM_004493 | *****        |
|                           |  | myeloperoxidase/MPO                                                   | 254600 | J02694    | 17q23.1      |
|                           |  | mitogen activated protein kinase associated protein kinase 2/MAPKAPK2 | 602006 | X75346    | *****        |
| Tau Phosphorylation State |  | protein phosphatase 2, structural/regulatory subunit A, beta/PPP2R1B  | 603113 | *****     | 11q22-q24    |
|                           |  | protein phosphatase 2, regulatory subunit B, alpha/PPP2R5A            | 601643 | NM_006243 | 1q41         |
|                           |  | protein phosphatase 2, regulatory subunit B, beta/PPP2R5B             | 601644 | NM_006244 | 11q13        |
|                           |  | protein phosphatase 2, regulatory subunit B, gamma/PPP2R5C            | 601645 | NM_002719 | 3p21         |
|                           |  | protein phosphatase 2, regulatory subunit B, delta/PPP2R1D            | 601646 | NM_006245 | 6p21.1       |
|                           |  | protein phosphatase 2, regulatory subunit B, epsilon/PPP2R1E          | 601647 | NM_006246 | 7p12-p11.2   |
|                           |  | Thimet oligopeptidase                                                 | 601117 | Z50115    | 19p13.3      |
|                           |  | alpha-1-antichymotrypsin/AAC1                                         | 107280 | NM_001085 | 14q32.1      |
|                           |  | apoptosis-related cysteine protease 1/caspase 1/CASP3                 | 600636 | NM_004346 | 4q35         |
|                           |  | alpha-2-macroglobulin/A2M                                             | 103950 | NM_000014 | 2p13.3-p12.3 |
| Catabolism                |  | apolipoprotein A1 of HDL/APOA1                                        | 107680 | NM_000039 | 11q23        |
|                           |  | apolipoprotein A4/APOA4                                               | 107690 | NM_000482 | 11q23        |
|                           |  | apolipoprotein C1/APOC1                                               | 107710 | NM_001645 | 19q13.2      |
|                           |  | apolipoprotein D/APOD                                                 | 107740 | NM_001647 | 3q26.2-qter  |
|                           |  | apolipoprotein E/APOE                                                 | 107741 | NM_000041 | 19q13.2      |
| Transport                 |  |                                                                       |        |           |              |
|                           |  |                                                                       |        |           |              |



|                                                                                   |        |                                                                     |                                               |              |              |
|-----------------------------------------------------------------------------------|--------|---------------------------------------------------------------------|-----------------------------------------------|--------------|--------------|
| Lipid Transport and Metabolism<br><i>(additional genes below in Inflammation)</i> | Uptake | apolipoprotein J/clustrin/APOJ/CLU                                  | 185430                                        | NM_001831    | 8p21-p12     |
|                                                                                   |        | low density lipoprotein receptor-related protein 1/LRP1             | 107770                                        | NM_002332    | 2q13.1-q13.2 |
|                                                                                   |        | low density lipoprotein receptor-related protein 2/LRP2             | 600073                                        | U33837       | 2q24-q31     |
|                                                                                   |        | low density lipoprotein receptor-related protein 5/LRP5             | 603506                                        | AF077820     | 11q13.4      |
|                                                                                   |        | low density lipoprotein receptor-related protein 8/LRP8             | 602600                                        | NM_004631    | 1p34         |
|                                                                                   |        | low density lipoprotein receptor-related protein-associated protein | 104225                                        | NM_002337    | 4p16.3       |
|                                                                                   |        | oxidized low density lipoprotein receptor/OLR1                      | 602601                                        | NM_002543    | 12p13-p12    |
|                                                                                   |        | very low density lipoprotein receptor/VLDLR                         | 192977                                        | S73732       | 9p24         |
|                                                                                   |        | sortilin related receptor/SORL1                                     | 602005                                        | U60975       | 1q23.2-q24.2 |
|                                                                                   |        | plasma cholesterol ester transfer protein/CETP                      | 118470                                        | NM_000078    | 16q21        |
|                                                                                   |        | phospholipid transfer protein/PLTP                                  | 172425                                        | NM_006227    | 20q12-q13.1  |
|                                                                                   |        | sterol-O-acyl transferase 1/SOAT1                                   | 102642                                        | L21934       | 1q25         |
|                                                                                   |        | sterol-O-acyl transferase 2/SOAT2                                   | 601311                                        | *****        | chr. 12      |
|                                                                                   |        | HMGCoA reductase/HMGCR                                              | 142910                                        | NM_000859    | 5q13.3-q14   |
|                                                                                   |        | pyruvate dehydrogenase complex E1-alpha subunit/PDHA1               | 312170                                        | L48690       | Xp22.2-p22.1 |
|                                                                                   |        | pyruvate dehydrogenase (lipoamide) beta subunit/PDHB                | 179060                                        | NM_000925    | 3p13-q23     |
|                                                                                   |        | Metabolism                                                          | pyruvate dehydrogenase complex E3 subunit/DLD | 246900       | NM_000108    |
| sialyltransferase 8/GD3                                                           | 601123 |                                                                     | NM_003034                                     | 2p12.1-p11.2 |              |

|                |                                                                                                                                          |        |           |              |
|----------------|------------------------------------------------------------------------------------------------------------------------------------------|--------|-----------|--------------|
| Myelination    | hexosaminidase A (alpha polypeptide)/HEXA                                                                                                | 272800 | NM_000520 | 15q23-q24    |
|                | hexosaminidase B (beta)                                                                                                                  | 268800 | M34906    | 5q13         |
| Myelination    | lysosomal acid beta-galactosidase                                                                                                        | 230500 | S55851    | 3p21.33      |
|                | GM2 ganglioside activator protein/GM2A                                                                                                   | 272750 | NM_000405 | 5q31.3-q33.1 |
| Myelination    | UDP-Gal:betaGlcNAc beta 1,3-galactosyltransferase, polypeptide 2/B3GALT2                                                                 | 603095 | NM_003783 | 6p21.3       |
|                | myelin proteolipid                                                                                                                       | 312080 | M27110    | Xq22         |
| Receptors      | Folate Receptor Alpha/FOLR1                                                                                                              | 136430 | M28099    | 1q13.3-q13.5 |
|                | Folate Receptor Beta/FOLR2                                                                                                               | 136425 | AF000380  | 1q13.3-q13.5 |
| Receptors      | Folate Receptor Gamma/FOLR3                                                                                                              | 602469 | Z32564    | *****        |
|                | Folate Transporter (SLC19A1)                                                                                                             | 600424 | U19720    | 21q22.3      |
| Transporter    | Vitamin B12 binding protein                                                                                                              | 275350 | NM_000355 | 22q11.2-qter |
|                | folylpolyglutamate synthetase/FPGS                                                                                                       | 136510 | M98045    | 9cen-q34     |
| Glutaminati on | gamma-glutamyl hydrolase/GGH                                                                                                             | 601509 | U55206    | *****        |
|                | Methylenetetrahydrofolate reductase/MTHFR                                                                                                | 236250 | U09806    | 1p36.3       |
| Glutaminati on | Dihydrofolate reductase/DHFR                                                                                                             | 126060 | J00140    | 5q11.2-q13.2 |
|                | 5,10-methylenetetrahydrofolate dehydrogenase, 5,10-methylenetetrahydrofolate cyclohydrolase, 10-formyltetrahydrofolate synthetase/MTHFD1 | 172460 | NM_005956 | 14q24        |
| Glutaminati on | 5,10-methenyltetrahydrofolate synthetase (5-formyltetrahydrofolate cyclo-ligase)/MTHFS                                                   | 604197 | NM_006441 | Chr. 15      |

| Folate<br>Metabolism                 | Metabolism                                                                                  |        |           |              |  |
|--------------------------------------|---------------------------------------------------------------------------------------------|--------|-----------|--------------|--|
|                                      |                                                                                             |        |           |              |  |
|                                      | phosphoribosylglycinamide<br>formyltransferase,<br>phosphoribosylglycinamide<br>synthetase, | 138440 | NM_000819 | 21q22.1      |  |
|                                      | phosphate hydrolase 1/FOH1                                                                  | 600934 | NP_004467 | 11q14        |  |
|                                      | 6-pyruvoyl tetrahydrobiopterin<br>synthase/PTPS                                             | 261640 | Q03393    | 1q22.3-q23.3 |  |
|                                      | serine hydroxymethyltransferase 1<br>(soluble)/SHMT1                                        | 182144 | NM_004169 | 17p11.2      |  |
|                                      | serine hydroxymethyltransferase 2<br>(mitochondrial)/SHMT2                                  | 138450 | NM_005412 | 12q13        |  |
|                                      | Glycine aminotransferase/glycine<br>cleavage T protein/GAT                                  | 238310 | NM_000481 | 3p21.2-p21.1 |  |
|                                      | 5-methyltetrahydrofolate-<br>homocysteine<br>methyltransferase/methionine<br>glutamate      | 156570 | NM_000254 | 1q43         |  |
|                                      | formiminotransferase/dihydrofolate<br>synthetase                                            | 229100 | *****     | *****        |  |
| Carbon Unit<br>Activation<br>for SAM | methionine adenosyltransferase I,<br>alpha/MAT1A                                            | 250850 | NM_000429 | 10q22        |  |
|                                      | methionine adenosyltransferase II,<br>alpha/MAT2A                                           | 601468 | NM_005911 | 2p11.2       |  |

Table 3. ADME and Toxicology Gene List

| Class | Pathway | Function | Name                  | OMIM   | GID       | Locus    |
|-------|---------|----------|-----------------------|--------|-----------|----------|
|       |         |          | sucrase-isomaltase/SI | 222900 | NM_001041 | 3q25-q26 |

|                     |                                                           |        |           |               |
|---------------------|-----------------------------------------------------------|--------|-----------|---------------|
| <b>Glycosidases</b> | maltase-glucoamylase/alpha-glucosidase/MGAM               | 154360 | NM_004668 | Chr.7         |
|                     | lactase-phlorizin hydrolase/LPH/lactase/LCT               | 603202 | NM_002299 | 2q21          |
|                     | salivary amylase A/AMY1A                                  | 104700 | NM_004038 | 1p21          |
|                     | salivary amylase B/AMY1B                                  | 104701 | *****     | 1p21          |
|                     | salivary amylase C/AMY1C                                  | 104702 | *****     | 1p22          |
|                     | pancreatic amylase A/AMY2A                                | 104650 | X07057    | 1p21          |
|                     | pancreatic amylase B/AMY2B                                | 104660 | *****     | 1p21          |
|                     | dipeptidylpeptidase IV/CD26/ADA complexing protein 2/DPP4 | 102720 | NM_001935 | 2q23          |
| <b>Proteases</b>    | pepsinogen A/PGA/PG                                       | 169700 | AH001519  | 11q13         |
|                     | pepsinogen, group 3/PGA3                                  | 169710 | *****     | 11q13         |
|                     | pepsinogen C/PGC                                          | 169740 | J04443    | 6p21.3-p21.1  |
|                     | kallikrein 1/KLK1                                         | 147910 | AH002853  | 19q13.2-q13.4 |
|                     | chymotrypsin-like protease                                | 118888 | X71875    | 16q22.1       |
|                     | trypsinogen 1/TRY1/protease, serine 1/PRSS1               | 276000 | NM_002769 | 7q35          |
|                     | trypsinogen 1/TRY2/protease, serine 2/PRSS2               | 601564 | NM_002770 | 7q35          |
|                     | trypsinogen 1/TRY3/protease, serine 3/PRSS3               | *****  | NM_002771 | *****         |
|                     | enterokinase 1/TRY3/protease, serine 7/PRSS7              | 226200 | NM_002772 | 21q21         |
|                     |                                                           |        |           |               |
|                     |                                                           |        |           |               |
|                     |                                                           |        |           |               |

|                                         |                                 |                                                                    |        |           |               |
|-----------------------------------------|---------------------------------|--------------------------------------------------------------------|--------|-----------|---------------|
| <b>Gastrointestinal Drug Metabolism</b> | <b>Proteases and Peptidases</b> | chymotrypsinogen 1/CTRB1                                           | 118890 | NM_001906 | 16q23.2-q23.3 |
|                                         |                                 | carboxypeptidase A1/CPA1                                           | 114850 | NM_001868 | 7q32-qter     |
|                                         |                                 | carboxypeptidase A2/CPA2                                           | 600688 | NM_001869 | *****         |
|                                         |                                 | carboxypeptidase Z/CPZ                                             | 603105 | NM_003652 |               |
|                                         |                                 | elastase 1/ELA1                                                    | 130120 | D00158    | 12q13         |
|                                         |                                 | renal microsomal dipeptidase/DPEPI (b-lactam ring hydrolysis)      | 179780 | NM_004413 | 16q24.3       |
|                                         |                                 | tripeptidyl peptidase II/TPP2                                      | 190470 | NM_003291 | 13q32-q33     |
|                                         |                                 | protease inhibitor 1/alpha-1-antitrypsin/AAT/PI                    | 107400 | NM_000295 | 14q32.1       |
|                                         |                                 | protease inhibitor/alpha-1-antichymotrypsin/AAC1                   | 107280 | NM_001085 | 14q32.1       |
|                                         |                                 | protease inhibitor 1 (alpha-1-antitrypsin)-like/PIL                | 107410 | NM_006220 | 14q32.1       |
| <b>Lipases</b>                          |                                 | Carboxyl ester lipase (bile salt-stimulated lipase)/CEL            | 114840 | M85201    | 9q34.3        |
|                                         |                                 | Carboxyl ester lipase-like (bile salt-stimulated lipase-like)/CELL | 114841 | NM_001808 | 9q34.3        |
|                                         |                                 | Pancreatic colipase/CLPS                                           | 120105 | M95529    | 6pter-p21.1   |
|                                         |                                 | Pancreatic triglyceride lipase/PNLIP                               | 246600 | AH003527  | 10q26.1       |
|                                         |                                 | Lipoprotein lipase/LPL                                             | 238600 | NM_000237 | 8p22          |
|                                         |                                 | Hepatic triglyceride lipase/LIPC                                   | 151670 | AH005429  |               |

|                        |                                                                          |        |           |               |
|------------------------|--------------------------------------------------------------------------|--------|-----------|---------------|
| <b>Oxidases</b>        | salivary peroxidase/SAPX                                                 | 170990 | U39573    | *****         |
|                        | alcohol dehydrogenases 6/ADH6                                            | 103735 | NM_000672 | 15q26         |
| <b>Esterases</b>       | paraoxonase 2/PON2                                                       | 602447 | L48513    | 7q21.3        |
| <b>Phosphatases</b>    | intestinal alkaline phosphatase/ALPI                                     | 171740 | NM_001631 | 2q36.3-q37.1  |
|                        | tissue non-specific alkaline phosphatase/liver alkaline phosphatase/ALPL | 171760 | NM_000478 | 1p36.1-p34    |
|                        | serum albumin/ALB                                                        | 103600 | NM_000477 | 4q11-q13      |
| <b>Blood Transport</b> | alpha fetoprotein/AFP                                                    | 104150 | NM_001134 | 4q11-q13      |
|                        | alpha albumin/afamin/AFM/ALB2                                            | 104145 | NM_001133 | 4q11-q13      |
|                        | vitamin D-binding protein/group-specific component/GC                    | 139200 | AH004448  | 4q12          |
|                        | orosomucoid 1/alpha 1 acid glycoprotein/ORM1                             | 138600 | M13692    | 9q34.1-q34.3  |
|                        | orosomucoid 2/alpha 1 acid glycoprotein, type 2/ORM2                     | 138610 | NM_000608 | 9q34.1-q34.3  |
|                        | transthyretin (prealbumin, amyloidosis type I)/TTR                       | 176300 | NM_000371 | 18q11.2-q12.1 |
|                        | thyroxin-binding globulin/TBG                                            | 314200 | NM_000354 | Xq22.2        |
|                        | corticosteroid binding globulin precursor/CBG                            | 122500 | NM_001756 | 14q32.1       |
|                        | sex hormone-binding globulin/SHBG                                        | 182205 | X16349    | 17p13-p12     |
|                        |                                                                          |        |           |               |
| <b>Drug Binding</b>    |                                                                          |        |           |               |

|                              |                                                                                     |        |               |                  |
|------------------------------|-------------------------------------------------------------------------------------|--------|---------------|------------------|
|                              | mannose-binding lectin,<br>soluble/MBL2                                             | 154545 | NM_00024<br>2 | 10q11.2-<br>q21  |
| <b>Bile Acid<br/>Binders</b> | Hepatic fatty acid binding<br>protein/FABP1                                         | 134650 | *****         | 2p11             |
|                              | Intestinal fatty acid binding<br>protein/FABP2                                      | 134640 | NM_00013<br>4 | 4q28-q31         |
|                              | Muscle fatty acid binding<br>protein/mammary-derived growth<br>inhibitor/MDGI/FABP3 | 134651 | NM_00410<br>2 | 1p33-p31         |
|                              | Adipocyte fatty acid binding<br>protein/FABP4                                       | 600434 | NM_00144<br>2 | 8q21             |
|                              | Ileal fatty acid binding protein/FABP6                                              | 600422 | U19869        | 5q23-q35         |
|                              | Brain fatty acid binding<br>protein/FABP7                                           | 602965 | D88648        | 6q22-q23         |
|                              | Adipocyte long chain fatty acid<br>transport protein/FATP                           | 600691 | *****         | *****            |
|                              | Retina-specific ATP binding cassette<br>transporter/ABCR                            | 601691 | NM_00035<br>0 | 1p21-p13         |
|                              | ATP binding cassette 1/ABC1                                                         | 600046 | AJ012376      | 9q22-q31         |
|                              | ATP binding cassette 2/ABC2                                                         | 600047 | U18235        | 9q34             |
|                              | ATP binding cassette 3/ABC3                                                         | 601615 | NM_00108<br>9 | 16p13.3          |
|                              | ATP binding cassette 7/ABC7                                                         | 300135 | AB005289      | Xq13.1-<br>q13.3 |
|                              | ATP binding cassette 8/ABC8                                                         | 603076 | AF038175      | 21q22.3          |
|                              | ATP-binding cassette 50/ABC50                                                       | 603429 | AF027302      | 6p21.33          |
|                              | Placenta-specific ATP-binding<br>cassette transporter/ABCP                          | 603756 | NM_00482<br>7 | 4q22             |

|                                                                |        |           |           |
|----------------------------------------------------------------|--------|-----------|-----------|
| cystic fibrosis transmembrane conductance regulator/CFTR       | 602421 | NM_000492 | 7q31.2    |
| adrenoleukodystrophy/adrenomyeloneuropathy/ALD                 | 300100 | NM_000033 | Xq28      |
| adrenoleukodystrophy related protein/ALDR                      | 601081 | U28150    | 12q11-q12 |
| sulfonylurea receptor (hyperinsulinemia)/SUR                   | 600509 | NM_000352 | 11p15.1   |
| peroxisomal membrane protein 1/PXMP1                           | 170995 | NM_002858 | 1p22-p21  |
| peroxisomal membrane protein 1-like/PXMP1L                     | 603214 | NM_005500 | 14q24.3   |
| antigen peptide transporter 1/MHC 1/TAP1                       | 170260 | NM_000593 | 6p21.3    |
| antigen peptide transporter 2/MHC 2/TAP2                       | 170261 | NM_000544 | 6p21.3    |
| multidrug resistance associated protein MRP1                   | 158343 | L05628    | 16p13.1   |
| multidrug resistance associated protein MRP2/CMOAT             | 601107 | NM_000392 | 10q24     |
| ATP-binding cassette, sub-family C (CFTR/MRP), member 3/CMOAT2 | *****  | NM_003786 | *****     |
| ATP-binding cassette, sub-family C (CFTR/MRP), member 4/MOATB  | *****  | NM_005845 | *****     |
| ATP-binding cassette, sub-family C (CFTR/MRP), member 5/SMRP   | *****  | NM_005688 | *****     |
| ATP-binding cassette, sub-family C (CFTR/MRP), member 9/SUR2   | 601439 | NM_005691 | *****     |

### ABC Transporters



**Absorption  
and  
Distribution**

|                                                          |        |           |              |
|----------------------------------------------------------|--------|-----------|--------------|
| multidrug resistance protein MDR1                        | 171050 | X96395    | 7q21.1       |
| multidrug resistance protein MDR3/P-glycoprotein 3/PGY3  | 602347 | X06181    | 7q21.1       |
| anthracycline resistance-related protein/ARA             | 603234 | NM_001171 | 16p13.1      |
| bile salt export pump/BSEP                               | 603201 | NM_003742 | 2q24         |
| familial intrahepatic cholestasis 1/FIC1                 | 602397 | NM_005603 | 18q21        |
| Human sorcin/SRI                                         | 182520 | L12387    | 7q21.1       |
| Solute carrier family 1, member 1/SLC1A1 (glutamate)     | 133550 | U08989    | 9p24         |
| Solute carrier family 1, member 2/SLC1A2 (glutamate)     | 600300 | U03505    | 11p13-p12    |
| Solute carrier family 1, member 3/SLC1A3 (glutamate)     | 600111 | U03504    | 5p13         |
| Solute carrier family 1, member 4/SLC1A4 (glutamate)     | 600229 | NM_003038 | 2p15-p13     |
| Solute carrier family 1, member 5/SLC1A5 (neutral AA)    | 109190 | AF105230  | 19q13.3      |
| Solute carrier family 1, member 6/SLC1A6 (glutamate)     | 600637 | NM_005071 | *****        |
| Solute carrier family 2, member 1/SLC2A1/SGLT1 (glucose) | 182380 | NM_006516 | 22q13.1      |
| Solute carrier family 2, member 2/SLC2A2/GLUT2 (glucose) | 138160 | NM_006516 | 3q26.1-q26.3 |
| Solute carrier family 2, member 3/SLC2A3/GLUT3 (glucose) | 138170 | M20681    | 12p13.3      |

|                                                                   |        |           |             |
|-------------------------------------------------------------------|--------|-----------|-------------|
| Solute carrier family 2, member 4/SLC2A4/GLUT4 (glucose)          | 138190 | *****     | 17p13       |
| Solute carrier family 2, member 5/SLC2A5/GLUT5 (glucose)          | 138230 | NM_003039 | 1p36.2      |
| Solute carrier family 3 member 1/SLC3A1 (aa transporter)          | 104614 | *****     | 2p16.3      |
| Solute carrier family 5 member 1/SLC5A2 (glucose)                 | 182381 | *****     | 16p11.2     |
| Solute carrier family 5 member 3/SLC5A3 (myoinositol)             | 600444 | L38500    | 21q22       |
| Solute carrier family 5 member 6/SLC5A6 (folate, biotin, lipoate) | 604024 | *****     | 2p23        |
| Solute carrier family 6 member 1/SLC6A1 (GABA)                    | 137165 | X54673    | 3p25-p24    |
| Solute carrier family 6 member 2/SLC6A2 (noradrenalin)            | 163970 | NM_001043 | 16q12.2     |
| Solute carrier family 6 member 3/SLC6A3 (dopamine)                | 126455 | L24178    | 5p15.3      |
| Solute carrier family 6 member 4/SLC6A4 (serotonin)               | 182138 | X70697    | 17q11.1-q12 |
| Solute carrier family 6, member 5/SLC6A5 (glycine)                | 604159 | NM_004211 | *****       |
| Solute carrier family 6, member 6/SLC6A6 (taurine)                | 186854 | U16120    | 3p25-q24    |
| Solute carrier family 6, member 8/SLC6A8 (creatine)               | 300036 | NM_005629 | 300036      |
| Solute carrier family 6, member 9/SLC6A9 (glycine)                | 601019 | S70612    | 1p33        |

Drug Uptake

|                                                                 |        |           |               |
|-----------------------------------------------------------------|--------|-----------|---------------|
| Solute carrier family 6, member 10/SLC6A10 (creatine-testis)    | 601294 | *****     | 16p11.2       |
| Solute carrier family 6, member 12/SLC6A12 (GABA-betaine)       | 603080 | NM_003044 | 12p13         |
| Solute carrier family 7, member 1/SLC7A1 (cationic AA)          | 104615 | *****     | 13q12.3       |
| Solute carrier family 7, member 2/SLC7A2 (cationic AA)          | 601872 | D29990    | 8p22          |
| Solute carrier family 7, member 4/SLC7A4 (cationic AA)          | 603752 | *****     | 22q11.2       |
| Solute carrier family 7, member 5/SLC7A5 (neutral AA)           | 600182 | M80244    | 16q24.3       |
| Solute carrier family 7, member 7/SLC7A7 (dibasic AA)           | 603593 | Y18474    | 14q11.2       |
| Solute carrier family 7, member 9/SLC7A9 (neutral AA)           | 604144 | *****     | 19q13.1       |
| Solute carrier family 10, member 1/SLC10A1 (taurocholate)       | 182396 | NM_003049 | chr. 14       |
| Solute carrier family 10, member 2/SLC10A2 (taurocholate)       | 601295 | NM_000452 | 13q33         |
| Solute carrier family 11, member 1/SLC11A1 (?)                  | 600266 | AH002806  | 2q35          |
| Solute carrier family 11, member 2/SLC11A2 (iron)               | 600523 | L37347    | 12q13         |
| Solute carrier family 13, member 2/SLC13A2 (dicarboxylic acids) | 604148 | NM_003984 | 17p11.1-q11.1 |
| Solute carrier family 14, member 1/SLC14A1 (urea)               | 111000 | *****     | 18q11-q12     |

**Solute  
Antiporters**

|                                                                   |        |           |               |
|-------------------------------------------------------------------|--------|-----------|---------------|
| Solute carrier family 14, member 2/SLC14A2 (urea)                 | 601611 | X96969    | 18q12.1-q21.1 |
| Solute carrier family 15, member 1/SLC15A1 (peptides)             | 600544 | U13173    | 13q33-q34     |
| Solute carrier family 15, member 2/SLC15A2 (peptides)             | 602339 | S78203    | *****         |
| Solute carrier family 16, member 1/SLC16A1 (monocarboxylic acids) | 600682 | NM_003051 | 1p13.2-p12    |
| Solute carrier family 16, member 2/SLC16A2 (monocarboxylic acids) | 300095 | NM_006517 | Xq13.2        |
| Solute carrier family 16, member 3/SLC16A3 (monocarboxylic acids) | 603877 | NM_004207 | *****         |
| Solute carrier family 16, member 4/SLC16A4 (monocarboxylic acids) | 603878 | *****     | *****         |
| Solute carrier family 16, member 5/SLC16A5 (monocarboxylic acids) | 603879 | NM_004695 | *****         |
| Solute carrier family 16, member 6/SLC16A6 (monocarboxylic acids) | 603880 | NM_004694 | *****         |
| Solute carrier family 16, member 7/SLC16A7 (monocarboxylic acids) | 603654 | AF049608  | 12q13         |
| Solute carrier family 18, member 1/VAT1/SLC18A1 (monoamines)      | 193001 | L09118    | 10q25         |
| Solute carrier family 18, member 2/VAT2/SLC18A2 (monoamines)      | 193002 | *****     | 8p21.3        |
| Solute carrier family 18, member 3/VAT3/SLC18A3 (monoamines)      | 600336 | NM_003055 | 10q11.2       |
| Solute carrier family 19, member 1/SLC19A1 (reduced folate)       | 600424 | U19720    | 21q22.3       |

|                                                                                    |        |           |              |
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| Solute carrier family 19, member 2/SLC19A2 (thiamine)                              | 603941 | AF160186  | 1q23.2-q23.3 |
| Solute carrier family 21, member 2/SLC21A2 (prostaglandin)                         | 601460 | NM_005630 | 3q21         |
| Solute carrier family 21, member 3/SLC21A3 (organic anion)                         | 602883 | NM_005075 | 12p12        |
| Solute carrier family 22, member 1/SLC22A1 (organic cation)                        | 602607 | NM_003058 | 6q26         |
| Solute carrier family 22, member 1-like/SLC22A1L (organic cation)                  | 602631 | AF037064  | 11p15.5      |
| Solute carrier family 22, member 2/SLC22A2 (organic cation)                        | 602608 | NM_003058 | 6q26         |
| Solute carrier family 22, member 4/SLC22A4 (organic cation)                        | 604190 | NM_003059 | Chr. 5       |
| Solute carrier family 22, member 5/SLC22A5 (carnitine)                             | 603377 | NM_003060 | 5q33.1       |
| Solute carrier family 25, member 1/SLC25A1 (tricarboxylic acids) (mitochondrial)   | 190315 | X96924    | 22q11        |
| Solute carrier family 25, member 11/SLC25A11 (oxoglutarate/malate) (mitochondrial) | 604165 | NM_003562 | 17p13.3      |
| Solute carrier family 25, member 12/SLC25A12 (?) (mitochondrial)                   | 603667 | NM_003705 | *****        |
| Solute carrier family 25, member 13/SLC25A13 (?) (mitochondrial)                   | 603859 | *****     | 7q21.3       |

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|------------------------------------------------------------------------------|--------|-----------|---------------|
| Solute carrier family 25, member 15/SLC25A15 (ornithine) (mitochondrial)     | 603861 | *****     | 13q14         |
| Solute carrier family 25, member 16/SLC25A16 (ADP/ATP) (mitochondrial)       | 139080 | M31659    | 10q21.3-q22.1 |
| Solute carrier family 29, member 1/SLC29A1/ENT1 (nucleoside) (mitochondrial) | 602193 | NM_004955 | 6p21.2-p21.1  |
| Solute carrier family 29, member 2/SLC29A2/ENT2 (nucleoside) (mitochondrial) | 602110 | X86681    | 11q13         |
| Aryl hydrocarbon receptor nuclear translocator/ARNT                          | 126110 | NM_001668 | 1q21          |
| Aryl hydrocarbon receptor nuclear translocator-like/ARNTL                    | 602550 | NM_001178 | 11p15         |
| Aryl hydrocarbon receptor/AHR                                                | 600253 | NM_001621 | 7p15          |
| Nuclear receptor subfamily 1, group I, member 2/NR1I2                        | 603065 | NM_003889 | *****         |
| Constitutive androstane receptor, beta/orphan nuclear hormone receptor/CAR   | 603881 | NM_005122 | *****         |
| Nuclear receptor subfamily 1, group H, member 2/NR1H2                        | 600380 | U07132    | 19q13.3       |
| Retinoic acid receptor, alpha/RARA                                           | 180240 | NM_000964 | 17q12         |
| Retinoic acid receptor, beta/RARB                                            | 180220 | NM_000965 | 3p24          |

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|-------------------------------------------------------------------------------|--------|-----------|-------------|
| Retinoic acid receptor, gamma/RARG                                            | 180190 | M57707    | 12q13       |
| Retinoid X receptor alpha/RXRA                                                | 180245 | NM_005693 | 9q34.3      |
| Retinoid X receptor beta/RXRB                                                 | 180246 | X66424    | 6p21.3      |
| Retinoid X receptor gamma/RXRG                                                | 180247 | U38480    | 1q22-q23    |
| RAR-related orphan receptor A/RORA                                            | 600825 | NM_002943 | 15q21-q22   |
| RAR-related orphan receptor B/RORB                                            | 600825 | *****     | 15q21-q22   |
| RAR-related orphan receptor C/RORC                                            | 602943 | NM_005060 | 1q21        |
| cellular retinoic acid-binding protein, type 2/CRABP2                         | 180231 | *****     | 1q21.3      |
| glucocorticoid receptor/GRL                                                   | 138040 | NM_000176 | 5q31        |
| Peroxisome proliferative activated receptor, alpha/PPARA                      | 170998 | NM_005036 | 22q12-q13.1 |
| Peroxisome proliferative activated receptor, gamma/PPARG                      | 601487 | NM_005037 | 3p25        |
| Peroxisome proliferative activated receptor, delta/PPARD                      | 6E+05  | NM_006238 | 1q21.3      |
| cytochrome P450, subfamily I, polypeptide 1 (aryl hydrocarbon oxidase)/CYP1A1 | 108330 | NM_000499 | 15q22-q24   |
| cytochrome P450, subfamily I, polypeptide 2 (phenacetin metabolism)/CYP1A2    | 124060 | AH002667  | 15q22-qter  |
| cytochrome P450, subfamily IB, polypeptide 1 (dioxin inducible)/CYP1B1        | 601771 | NM_000104 | 2p22-p21    |

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|-------------------------------------------------------------------------------------------|--------|---------------|-------------------|
| cytochrome P450, subfamily II,<br>polypeptide 1 (phenobarbital<br>inducible)/CYP2A        | 123960 | X13897        | 19q13.2           |
| cytochrome P450, subfamily IIA,<br>polypeptide 6 (coumarin-7-<br>hydroxylase)/CYP2A6      | 122720 | NM_00076<br>2 | 19q13.2           |
| cytochrome P450, subfamily IIB<br>(phenobarbital inducible)/CYP2B                         | 123930 | M29874        | 19q13.2           |
| cytochrome P450, subfamily IIC,<br>polypeptide 8/CYP2C8                                   | 601129 | *****         | 10q24             |
| cytochrome P450, subfamily IIC,<br>polypeptide 9 (hydroxylation of<br>tolbutamide)/CYP2C9 | 601130 | *****         | 10q24             |
| cytochrome P450, subfamily IIC,<br>polypeptide 18/CYP2C18                                 | 601131 | *****         | 10q25             |
| cytochrome P450, subfamily IIC,<br>polypeptide 19 (mephenytoin 4-<br>hydroxylase)/CYP2C19 | 124020 | NM_00076<br>9 | 10q24.1-<br>q24.3 |
| cytochrome P450, subfamily IID,<br>polypeptide 6 (debrisoquine<br>hydroxylation)/CYP2D6   | 124030 | NM_00010<br>6 | 22q13.1           |
| cytochrome P450, subfamily IIE<br>(ethanol inducible)/CYP2E                               | 124040 | J02843        | 10q24.3-<br>qter  |
| cytochrome P450, subfamily IIF<br>(ethoxycoumarin monooxygenase),<br>polypeptide 1/CYP2F1 | 124070 | NM_00077<br>4 | 19q13.2           |
| cytochrome P450, subfamily IJ<br>(arachidonate epoxidase),<br>polypeptide 2/CYP2J2        | 601258 | NM_00077<br>5 | 1p31.3-<br>p31.2  |

**P450  
Cytochromes  
and  
Regulatory  
Factors**

**Cytochrome  
P450s**



|                                                                                           |        |               |            |
|-------------------------------------------------------------------------------------------|--------|---------------|------------|
| cytochrome P450, subfamily IIIA<br>(niphedipine oxidase), polypeptide<br>3/CYP3A4         | 124010 | NM_00077<br>6 | 7q22.1     |
| cytochrome P450, subfamily IVA<br>(fatty acid W-hydroxylase),<br>polypeptide 11/CYP4A11   | 601310 | NM_00077<br>8 | Chr.1      |
| cytochrome P450, subfamily IVB,<br>polypeptide 1/CYP4B1                                   | 124075 | NM_00077<br>9 | 1p34-p12   |
| cytochrome P450, subfamily IVF<br>(leukotriene B4-W-hydroxylase),<br>polypeptide 3/CYP4F3 | 601270 | NM_00089<br>6 | 19p13.2    |
| cytochrome P450, subfamily VIIA<br>(cholesterol 7-a-hydroxylase),<br>polypeptide 1/CYP7A1 | 118455 | M89803        | 8q11-q12   |
| cytochrome P450, subfamily VIIB<br>(oxysterol 7-a-hydroxylase),<br>polypeptide 1/CYP7B1   | 603711 | AF029403      | 8q21.3     |
| cytochrome P450, subfamily VIIB<br>(sterol 12-a-hydroxylase), polypeptide<br>1/CYP8B1     | 602172 | *****         | 3p21.3-p22 |
| cytochrome P450, subfamily XIA<br>(cholesterol side-chain<br>cleavage)/CYP11A             | 118485 | NM_00078<br>1 | 15q23-q24  |
| cytochrome P450, subfamily XIB,<br>polypeptide 2 (steroid 11-b-<br>hydroxylase)/CYP11B2   | 124080 | NM_00049<br>8 | 8q21       |
| cytochrome P450, subfamily XIX<br>(androgen aromatase)/CYP19                              | 107910 | NM_00010<br>3 | 15q21.1    |
| cytochrome P450, subfamily XXI<br>(sterol 21-a-hydroxylase)/CYP21                         | 201910 | M13936        | 6p21.3     |

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| Phase I Drug Metabolism<br>(oxidation and |                    | cytochrome P450, subfamily XXIV (25-hydroxyvitamin D 24-hydroxylase)/CYP24                            | 600125 | S67623    | 20q13.2-q13.3 |
|                                           |                    | cytochrome P450, subfamily XXVIA, polypeptide 1 (retinoic acid hydroxylase)/CYP26A1                   | 602239 | NM_000783 | 10q23-q24     |
|                                           |                    | cytochrome P450, subfamily XXVIA, polypeptide 1 (25-hydroxyvitamin D-1 $\alpha$ -hydroxylase)/CYP27A1 | 213700 | NM_000105 | 2q33-qter     |
|                                           |                    | adrenodoxin/ferredoxin 1/FDX1/ADX                                                                     | 103260 | NM_004109 | 11q22         |
|                                           |                    | adrenodoxin reductase/ferredoxin:NADP(+) reductase/FDXR/ADX                                           | 103270 | NM_004110 | 17q24-q25     |
|                                           |                    | cytochrome P450, subfamily XXVIB, polypeptide 1 (25-hydroxyvitamin D-1 $\alpha$ -hydroxylase)/CYP27B1 | 264700 | NM_000785 | 12q14         |
|                                           |                    | cytochrome P450, subfamily XLVI (cholesterol 24-hydroxylase)/CYP46                                    | 604087 | NM_006668 | 14q32.1       |
|                                           |                    | cytochrome P450, subfamily LI (lanosterol 14 $\alpha$ -demethylase)/CYP51                             | 601637 | U51692    | 7q21.2-q21.3  |
|                                           | Cofactor Synthesis | heme                                                                                                  | 603707 | AJ224328  | 6p21.3        |
|                                           |                    | heme                                                                                                  | 603708 | *****     | 5q11          |
|                                           | Alcohol            | alcohol dehydrogenases 1, alpha subunit/ADH1                                                          | 103700 | NM_000667 | 4q22          |
|                                           |                    | alcohol dehydrogenases 2, beta subunit/ADH2                                                           | 103720 | NM_000668 | 4q22          |
|                                           |                    | alcohol dehydrogenases 3, gamma subunit/ADH3                                                          | 103730 | M12272    | 4q22          |

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| <b>Dehydrogenases</b>                             | alcohol dehydrogenases 4/pi isozyme/ADH4                                        | 103740 | M15943    | 4q22     |
|                                                   | alcohol dehydrogenases 5/chi isozyme/ADH5                                       | 103710 | NM_000671 | 4q21-q25 |
|                                                   | alcohol dehydrogenases 6/ADH6                                                   | 103735 | NM_000672 | 15q26    |
|                                                   | alcohol dehydrogenases 7/ADH7                                                   | 600086 | AH006682  | 4q23-q24 |
| <b>Aldehyde Dehydrogenases</b>                    | aldehyde dehydrogenase 1/ALDH1 (liver cytosol)                                  | 100640 | AH002598  | 9q21     |
|                                                   | aldehyde dehydrogenase 2/ALDH2 (liver mitochondria)                             | 100650 | K03001    | 12q24.2  |
|                                                   | 3/acetaldehyde                                                                  | 100660 | M74542    | 17p11.2  |
|                                                   | 5/acetaldehyde                                                                  | 100670 | NM_000692 | 9p13     |
|                                                   | aldehyde dehydrogenase 5, member A1/succinic semialdehyde dehydrogenase/ALDH5A1 | 271980 | NM_001080 | 6p22     |
|                                                   | 6/acetaldehyde                                                                  | 600463 | NM_000693 | 15q26    |
|                                                   | 7/acetaldehyde                                                                  | 600466 | NM_000694 | 11q13    |
|                                                   | aldehyde dehydrogenase 8/ALDH8                                                  | 601917 | NM_000695 | chr. 11  |
|                                                   | aldehyde dehydrogenase 9/g-aminobutyraldehyde dehydrogenase/ALDH9               | 602733 | NM_000696 | 1q22-q23 |
|                                                   | aldehyde dehydrogenase 10/ALDH10                                                | 270200 | NM_000382 | 17p11.2  |
| <b>Pyridine Nucleotide-Linked Oxidoreductases</b> |                                                                                 |        |           |          |

|                                    |                                                                                     |        |               |           |
|------------------------------------|-------------------------------------------------------------------------------------|--------|---------------|-----------|
| <b>Aldo-Keto<br/>Reductases</b>    | Aldo-keto reductase family 1, member<br>A1/dihydrodiol<br>dehydrogenase/AKR1A1      | 103830 | NM_00606<br>6 | 1p33-p32  |
|                                    | Aldo-keto reductase family 1, member<br>C1/dihydrodiol<br>dehydrogenase/AKR1C1      | 600449 | NM_00135<br>3 | 10p15-p14 |
|                                    | Aldo-keto reductase family 1, member<br>C3/dihydrodiol<br>dehydrogenase/AKR1C3      | 603966 | NM_00373<br>9 | 10p15-p14 |
|                                    | Aldo-keto reductase family 1, member<br>C4/chlorodecone reductase/AKR1C4            | 600451 | *****         | 10p15-p14 |
|                                    | Aldo-keto reductase family 7, member<br>A2/aflatoxin aldehyde<br>reductase/AKR7A2   | 603418 | NM_00368<br>9 | *****     |
|                                    | Carbonyl reductase 1/CBR1                                                           | 114830 | NM_00175<br>7 | 21q22.12  |
|                                    | Carbonyl reductase 2/CBR2                                                           | *****  | *****         | chr. 11   |
|                                    | Carbonyl reductase 3/CBR3                                                           | 603608 | NM_00123<br>6 | 21q22.2   |
|                                    | Sepiapterin reductase (7,8-<br>dihydrobiopterin:NADP+<br>oxidoreductase)/SPR        | 182125 | NM_00312<br>4 | 2p14-p12  |
|                                    | Z-crystallin/quinone reductase/CRYZ                                                 | 123691 | L31521        | 1p31-p22  |
| <b>Quinone<br/>Oxidoreductases</b> | Z-crystallin-like/quinone reductase-<br>like/CRYZL1                                 | 603920 | NM_00511<br>1 | 21q22.1   |
|                                    | NAD(P)H menadione oxidoreductase<br>1, dioxin-<br>inducible/NMOR1/diaphorase 4/DIA4 | 125860 | NM_00090<br>3 | 16q22.1   |

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|--|--------------------------------------------------|---------------------------------------------------------------------|--------|---------------|-----------------|
|  |                                                  | NAD(P)H menadione oxidoreductase<br>2, dioxin-inducible/NMOR2       | 160998 | NM_00090<br>4 | 6pter-q12       |
|  |                                                  | Flavin-containing monooxygenase<br>1/FMO1                           | 136130 | NM_00202<br>1 | 1q23-q25        |
|  |                                                  | Flavin-containing monooxygenase<br>3/FMO3                           | 136132 | AH006707      | 1q23-q25        |
|  |                                                  | Flavin-containing monooxygenase<br>4/FMO4                           | 136131 | NM_00146<br>0 | 1q23-q25        |
|  |                                                  | Flavin-containing monooxygenase<br>5/FMO5                           | 603957 | NM_00146<br>1 | 1q21.1          |
|  | <b>Flavin-<br/>Dependent<br/>Oxidoreductases</b> | Monoamine Oxidase A; MAOA                                           | 309850 | M69226        | Xp11.23         |
|  |                                                  | Monoamine Oxidase B; MAOB                                           | 309860 | M69177        | Xp11.23         |
|  |                                                  | Xanthine dehydrogenase/XDH                                          | 278300 | NM_00037<br>9 | 2p23-p22        |
|  |                                                  | Aldehyde oxidase 1/AOX1                                             | 602841 | NM_00115<br>9 | 2q33            |
|  |                                                  | Copper-containing amine<br>oxidase/AOC3                             | 603735 | NM_00373<br>4 | 17q21           |
|  |                                                  | sulfite oxidase/SUOX                                                | 272300 | NM_00045<br>6 | *****           |
|  |                                                  | Dihydropyrimidine dehydrogenase (5-<br>fluorouracil detoxification) | 274270 | U09178        | 1p22            |
|  | <b>Peroxisome<br/>Proliferation</b>              | Peroxisome proliferative activated<br>receptor, alpha/PPARA         | 170998 | NM_00503<br>6 | 22q12-<br>q13.1 |
|  |                                                  | Peroxisome proliferative activated<br>receptor, gamma/PPARG         | 601487 | NM_00503<br>7 | 3p25            |
|  |                                                  | Peroxisome proliferative activated<br>receptor, delta/PPARD         | 180231 | NM_00623<br>8 | 1q21.3          |
|  |                                                  | peroxisome biogenesis factor 1/PEX1                                 | 602136 | AB008112      | 7q21-q22        |

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| <b>Peroxisome<br/>Synthesis</b>                     | peroxisomal membrane protein 3 (35kD)                                                          | 170993 | NM_000318 | 8q21.1   |
|                                                     | peroxisomal biogenesis factor 3/PEX3                                                           | 603164 | NM_003630 | *****    |
|                                                     | peroxisomal biogenesis factor 6/PEX6                                                           | 601498 | NM_000287 | 6p21.1   |
|                                                     | peroxisomal biogenesis factor 7/PEX7                                                           | 601757 | NM_000288 | 6q22-q24 |
|                                                     | peroxisomal biogenesis factor 10/PEX10                                                         | 602859 | *****     | *****    |
|                                                     | peroxisomal biogenesis factor 11A/PEX11A                                                       | 603866 | NM_003847 | *****    |
|                                                     | peroxisomal biogenesis factor 11B/PEX11B                                                       | 603867 | NM_003846 | *****    |
|                                                     | peroxisomal biogenesis factor 12/PEX12                                                         | 601758 | NM_000286 |          |
|                                                     | peroxisomal biogenesis factor 13/PEX13                                                         | 601789 | U71374    | 2p15     |
|                                                     | peroxisomal biogenesis factor 14/PEX14                                                         | 601791 | *****     | *****    |
| <b>Fatty Acid <math>\beta</math>-<br/>Oxidation</b> | peroxisomal farnesylated protein/PXFP                                                          | 600279 | NM_002857 | 1q22     |
|                                                     | Fatty acid CoA Ligase, long chain 1/FACL1                                                      | 152425 | *****     | 3q13     |
|                                                     | Fatty acid CoA Ligase, long chain 2/FACL2                                                      | 152426 | *****     | 4q34-q35 |
|                                                     | Fatty acid CoA Ligase, long chain 3/FACL3                                                      | 602371 | NM_004457 | 2q34-q35 |
|                                                     | Fatty acid CoA Ligase, long chain 4/FACL4                                                      | 300157 | NM_004458 | Xq22.3   |
|                                                     | Fatty acid CoA Ligase, very long chain 1/FACVL1                                                | 603247 | *****     | 15q21.2  |
|                                                     | Enoyl-CoA, hydratase/3-hydroxyacyl CoA dehydrogenase/EHHADH                                    | 261515 | NM_001966 | 3q27     |
|                                                     | hydroxyacyl-CoA dehydrogenase/3-ketoacyl-CoA thiolase/enoyl-CoA hydratase, alpha subunit/HADHA | 600890 | NM_000182 | 2p23     |
|                                                     | hydroxyacyl-CoA dehydrogenase/3-ketoacyl-CoA thiolase/enoyl-CoA hydratase, beta subunit/HADHB  | 143450 | NM_000183 | 2p23     |
|                                                     |                                                                                                |        |           |          |

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| <b>Oxidation</b>               | acyl-Coenzyme A oxidase 1/ACOX1 (peroxisomal)                                          | 264470 | NM_004035 | 17q25         |
|                                | acyl-Coenzyme A oxidase 2, branched chain/ACOX2 (peroxisomal)                          | 601641 | NM_003500 | 3p14.3        |
|                                | acyl-Coenzyme A dehydrogenase, C-2 to C-3 short chain precursor/ACADS (mitochondrial)  | 201470 | NM_000017 | 12q22-qter    |
|                                | acyl-Coenzyme A dehydrogenase, C-4 to C-12 straight chain/ACADM (mitochondrial)        | 201450 | NM_000016 | 1p31          |
|                                | acyl-Coenzyme A dehydrogenase, long chain/ACADL (mitochondrial)                        | 201460 | NM_001608 | 2q34-q35      |
|                                | hydroxyacyl-Coenzyme A dehydrogenase, type II/HADH2                                    | 602057 | NM_004493 | *****         |
|                                | enoyl-Coenzyme A hydratase 1/ECH1 (peroxisomal)                                        | 600696 | NM_001398 | 19q13         |
|                                | 3-prime-phosphoadenosine 5-prime-phosphosulfate synthase 1/PAPSS1                      | 603262 | NM_005443 | 4q            |
|                                | Phenol-preferring sulfotransferase, family 1A, member 1/SULT1A1                        | 171150 | NM_001055 | 16p12.1-p11.2 |
|                                | Phenol-preferring sulfotransferase, family 1A, member 2/SULT1A2                        | 601292 | NM_001054 | 16p12.1-p11.2 |
| <b>Sulfate Unit Activation</b> | Phenol-preferring sulfotransferase, family 1A, member 3/SULT1A3                        | 600641 | L19956    | 16p11.2       |
|                                | Sulfotransferase, family 1C, member 3/SULT1C1                                          | 602385 | U66036    | 2q11.1-q11.2  |
|                                | Dehydroepiandrosterone (DHEA)-preferring sulfotransferase, family 2A, member 1/SULT2A1 | 125263 | NM_003167 | 19q13.3       |

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| <b>Sulfation</b> | Sulfotransferase, family 2B, member 1/SULT2B1                                       | 604125 | NM_004605 | 19q13.3       |
|                  | Estrogen-prefering sulfotransferase/STE                                             | 600043 | NM_005420 | 4q13.1        |
|                  | N-deacetylase/N-sulfotransferase (heparan glucosaminyl)/NDST1                       | 600853 | U18918    | 5q32-q33.3    |
|                  | N-deacetylase/N-sulfotransferase (heparan glucosaminyl)/NDST2                       | 603268 | NM_003635 | 10q22         |
|                  | N-deacetylase/N-sulfotransferase (heparan glucosaminyl)/NDST3                       | 603950 | NM_004784 | *****         |
|                  | Carbohydrate sulfotransferase 1 (chondroitin 6/keratan)/CHST1                       | 603797 | NM_003654 | 11p11.2-p11.1 |
|                  | Carbohydrate sulfotransferase 2 (chondroitin 6/keratan)/CHST2                       | 603798 | *****     | 7q31          |
|                  | Carbohydrate sulfotransferase 3 (chondroitin 6/keratan)/CHST3                       | 603799 | NM_004273 | *****         |
|                  | Cerebroside sulfotransferase (3'-phosphoadenylylsulfate:galactosylceramide 3'')/CST | 602300 | NM_004861 | *****         |
|                  | Heparan sulfate (glucosamine) 3-O-sulfotransferase 1/HS3ST1                         | 603244 | NM_005114 | *****         |
|                  | Heparan sulfate (glucosamine) 3-O-sulfotransferase 2/HS3ST2                         | 604056 | NM_006043 | 16p12         |
|                  | Heparan sulfate (glucosamine) 3-O-sulfotransferase 3A1/HS3ST3A1                     | 604057 | NM_006042 | 17p12-p11.2   |
|                  | Heparan sulfate (glucosamine) 3-O-sulfotransferase 3B1/HS3ST3B1                     | 604058 | NM_006041 | 17p12-p11.2   |
|                  | Heparan sulfate (glucosamine) 3-O-sulfotransferase 4/HS3ST4                         | 604059 | AF105378  | 16p11.2       |



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| Sulphydrylation                | Methylguanine methyltransferase (O6-alkylguanine detoxification) | 156569 | M29971    | 10q26        |
|                                | thiotransferase/rhodanese/TST (amide detoxification)             | 180370 | D87292    | 22q11.2-qter |
| UDP-Glycosyltransferases       | UDP glycosyltransferase 1/UGT1                                   | 191740 | NM_001072 | Chr. 12      |
|                                | UDP glycosyltransferase family 2, member B4/UGT2B4               | 600067 | NM_001073 | 4q13         |
|                                | UDP glycosyltransferase family 2, member B7/UGT2B7               | 600068 | NM_001074 | 1q14         |
|                                | UDP glycosyltransferase family 2, member B10/UGT2B10             | 600070 | NM_001075 | *****        |
|                                | UDP glycosyltransferase family 2, member B15/UGT2B15             | 600069 | U06641    | 4q13         |
|                                | UDP glycosyltransferase family 2, member B17/UGT2B17             | 601903 | NM_001077 | 1q14         |
|                                | UDP glycosyltransferase 8/UGT8                                   | 601291 | U30930    | 4q26         |
|                                | UDP-glucuronosyltransferase                                      | 218800 | AJ005162  | Chr. 2       |
|                                | methionine adenosyltransferase I, alpha/MAT1A                    | 250850 | NM_000429 | 10q22        |
|                                | methionine adenosyltransferase II, alpha/MAT2A                   | 601468 | NM_005911 | 2p11.2       |
| Carbon Unit Activation for SAM | Folate Receptor Alpha/FOLR1                                      | 136430 | M28099    | 1q13.3-q13.5 |
|                                | Folate Receptor Beta/FOLR2                                       | 136425 | AF000380  | 1q13.3-q13.5 |
|                                | Folate Receptor Gamma/FOLR3                                      | 602469 | Z32564    | *****        |
|                                | Folate Transporter (SLC19A1)                                     | 600424 | U19720    | 21q22.3      |
|                                | Vitamin B12 binding protein                                      | 275350 | NM_000355 | 22q11.2-qter |
|                                | folypolyglutamate synthetase/FPGS                                | 136510 | M98045    | 9cen-q34     |
|                                | gamma-glutamyl hydrolase/GGH                                     | 601509 | U55206    | *****        |

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| <b>Conjugation</b> | <b>Carbon Unit<br/>Activation<br/>for Folate</b> | Methylenetetrahydrofolate reductase/MTHFR                                               | 236250 | U09806    | 1p36.3       |
|                    |                                                  | Dihydrofolate reductase/DHFR                                                            | 126060 | J00140    | 5q11.2-q13.2 |
|                    |                                                  | 5,10-methylenetetrahydrofolate dehydrogenase, 5,10-                                     |        |           |              |
|                    |                                                  | methylenetetrahydrofolate cyclohydrolase, 10-                                           |        |           |              |
|                    |                                                  | formyltetrahydrofolate synthetase/MTHFD1                                                | 172460 | NM_005956 | 14q24        |
|                    |                                                  | 5,10-methylenetetrahydrofolate synthetase (5-formyltetrahydrofolate cyclo-ligase)/MTHFS | 604197 | NM_006441 | Chr. 15      |
|                    |                                                  | phosphoribosylglycinamide formyltransferase,                                            |        |           |              |
|                    |                                                  | phosphoribosylglycinamide synthetase,                                                   |        |           |              |
|                    |                                                  | phosphoribosylaminoimidazole                                                            | 138440 | NM_000819 | 21q22.1      |
|                    |                                                  | folate hydrolase 1/FOH1                                                                 | 600934 | NP_004467 | 11q14        |
|                    |                                                  | 6-pyruvoyl tetrahydrobiopterin synthase/PTPS                                            | 261640 | Q03393    | 1q22.3-q23.3 |
|                    |                                                  | serine hydroxymethyltransferase 1 (soluble)/SHMT1                                       | 182144 | NM_004169 | 17p11.2      |
|                    |                                                  | serine hydroxymethyltransferase 2 (mitochondrial)/SHMT2                                 | 138450 | NM_005412 | 12q13        |
|                    |                                                  | Glycine aminotransferase/glycine cleavage T protein/GAT                                 | 238310 | NM_000481 | 3p21.2-p21.1 |
|                    |                                                  | 5-methyltetrahydrofolate-homocysteine                                                   |        |           |              |
|                    |                                                  | methyltransferase/methionine                                                            | 156570 | NM_000254 | 1q43         |

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| <b>Phase II<br/>Drug<br/>Metabolism<br/>(conjugation<br/>and<br/>catabolism)</b> |                                                           | glutamate<br>formiminotransferase/dihydrofolate<br>synthetase                         | 229100 | *****     | *****        |
|                                                                                  | <b>Methylation</b>                                        | catechol-O-methyltransferase/COMT                                                     | 116790 | NM_000754 | 22q11.2      |
|                                                                                  |                                                           | phenylethanolamine N-methyltransferase/PNMT                                           | 171190 | NM_002686 | 17q21-q22    |
|                                                                                  |                                                           | nicotinamide N-methyltransferase/NNMT                                                 | 600008 | NM_006169 | 11q23.1      |
|                                                                                  | <b>Carbon Unit<br/>Activation<br/>for Acetyl-<br/>CoA</b> | Thiopurine methyltransferase (6-mercaptopurine detoxification)                        | 187680 | U12387    | 6p22.3       |
|                                                                                  |                                                           | pyruvate dehydrogenase E1-alpha subunit/PDHA1                                         | 312170 | L48690    | Xp22.2-p22.1 |
|                                                                                  |                                                           | pyruvate dehydrogenase (lipoamide) beta/PDHB                                          | 179060 | NM_000925 | 3p13-q23     |
|                                                                                  |                                                           | pyruvate dehydrogenase complex, lipoyl-containing component X/E3-binding protein/PDX1 | 245349 | NM_003477 | 11p13        |
|                                                                                  | <b>Acylation</b>                                          | pyruvate dehydrogenase complex E3 subunit/DLD                                         | 246900 | NM_000108 | 7q31-q32     |
|                                                                                  |                                                           | sterol-O-acyl transferase 1/SOAT1                                                     | 102642 | L21934    | 1q25         |
|                                                                                  |                                                           | sterol-O-acyl transferase 2/SOAT2                                                     | 601311 | *****     | chr. 12      |
|                                                                                  |                                                           | N-acetyltransferase 1/arylamine acetylase 1/NAT1                                      | 108345 | NM_000662 | 8p23.1-p21.3 |
|                                                                                  |                                                           | N-acetyltransferase 2/arylamine acetylase 2/NAT2                                      | 243400 | NM_000015 | 8p23.1-p21.3 |
|                                                                                  |                                                           | cystathionine-beta-synthase/CBS                                                       | 236200 | NM_000071 | 21q22.3      |

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| <b>Glutathione Synthesis</b>   | cystathionase/cystathionine gamma-lyase/CTH                                               | 219500 | NM_001902 | Chr.16   |
|                                | glutamate-cysteine ligase (gamma-glutamyl/cysteine synthetase), catalytic (72.8kD)/GLCLC  | 230450 | NM_001498 | 6p12     |
|                                | glutamate-cysteine ligase (gamma-glutamyl/cysteine synthetase), regulatory (30.8kD)/GLCLR | 601176 | NM_002061 | 1p22.1   |
|                                | glutathione synthetase/GSS                                                                | 601002 | NM_000178 | 20q11.2  |
|                                | Glutathione-S-transferase 6                                                               | 138391 | *****     | *****    |
| <b>Glutathione Transferase</b> | Glutathione-S-transferase, alpha 1/GSTA1                                                  | 138359 | L13269    | 6p12.2   |
|                                | Glutathione-S-transferase, alpha 2/GSTA2                                                  | 138360 | M15872    | 6p12.2   |
|                                | Glutathione-S-transferase, kappa 1/GSTK1                                                  | 602321 | *****     | *****    |
|                                | Glutathione-S-transferase 1/MGST1 (microsomal)                                            | 138330 | AH003674  | Chr.12   |
|                                | Glutathione-S-transferase 2/MGST2 (microsomal)                                            | 601733 | NM_002413 | 4q28-q31 |
|                                | Glutathione-S-transferase, mu 1-like/GSTM1L                                               | 138270 | *****     | Chr. 3   |
|                                | Glutathione-S-transferase, mu 1/GSTM1                                                     | 138350 | J03817    | 1p13.3   |
|                                | Glutathione-S-transferase, mu 2/GSTM2 (muscle)                                            | 138380 | NM_000848 | 1p13.3   |
|                                | Glutathione-S-transferase, mu 3/GSTM3 (brain)                                             | 138390 | NM_000849 | 1p13.3   |
|                                | Glutathione-S-transferase, mu 4/GSTM4                                                     | 138333 | NM_000850 | 1p13.3   |
|                                |                                                                                           |        |           |          |
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|                  | Glutathione-S-transferase, mu 5/GSTM5 (brain/lung)                        | 138385 | NM_000851 | 1p13.3        |
|                  | Glutathione-S-transferase, pi/GSTP1                                       | 134660 | NM_000852 | 11q13         |
|                  | Glutathione-S-transferase, theta 1/GSTT1                                  | 600436 | NM_000853 | 22q11.2       |
|                  | Glutathione-S-transferase, theta 2/GSTT2                                  | 600437 | NM_000854 | 22q11.3       |
|                  | Glutathione-S-transferase, zeta 1/maleylacetoacetate isomerase/MAAI/GSTZ1 | 603758 | NM_001513 | 14q24.3       |
|                  | Gamma-glutamyltranspeptidase 1/GGT1                                       | 231950 | J04131    | 22q11.1-q11.2 |
|                  | Gamma-glutamyltranspeptidase 2/GGT2                                       | 137181 | AH002728  | 22q11.1       |
|                  | Gamma-glutamyltransferase-like activity 1/GGTLA1                          | 137168 | NM_004121 | *****         |
|                  | paraoxonase 1/PON1 (arylesterase)                                         | 168820 | AH004193  | 7q21.3        |
|                  | paraoxonase 2/PON2                                                        | 602447 | L48513    | 7q21.3        |
| <b>Esterases</b> | paraoxonase 3/PON3                                                        | 602720 | L48516    | 7q21.4        |
|                  | esterase C/ESC (acetyl esterase)                                          | 133270 | *****     | *****         |
|                  | esterase A4/ESA4                                                          | 133220 | *****     | 11q13-q22     |
|                  | esterase B/buteryl esterase/ESB (erythrocyte)                             | 133260 | *****     | *****         |
|                  | esterase B3/ESB3                                                          | 133290 | *****     | Chr.16        |
|                  | esterase A5/A7/acetylsterease/ESA5/ESA7 (brain)                           | 133230 | *****     | *****         |
|                  | acetylcholinesterase/ACHE                                                 | 100740 | M55040    | 7q22          |
|                  |                                                                           |        |           |               |
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| <b>Hydratases<br/>and Lyases</b> | butyrylcholinesterase 1/serum<br>cholinesterase 1/BCHE1                    | 177400 | NM_0000553q26.1-q26.2 |              |
|                                  | butyrylcholinesterase 2/serum<br>cholinesterase 2/BCHE2                    | 177500 | *****                 | 2q33-q35     |
|                                  | egaseyn/esterase 22                                                        | 129905 | AF177775              | *****        |
|                                  | neuropathy target esterase/NTE                                             | 603197 | NM_006702             | 19p          |
|                                  | carboxylesterase 1/serine<br>esterase/CES1 (hepatic)                       | 114835 | NM_001266             | 16q13-q22.1  |
|                                  | arylacetamide deacetylase/AADAC                                            | 600338 | NM_001086             | 3q21.3-q25.2 |
|                                  | acyl-CoA thioester hydrolase 1, long<br>chain/acyl-CoA thioesterase 1/ACT1 | 602586 | *****                 | *****        |
|                                  | acyl-CoA thioester hydrolase 2, long<br>chain/acyl-CoA thioesterase 2/ACT2 | 602587 | *****                 | *****        |
|                                  | esterase D/ESD                                                             | 133280 | M13450                | 13q14.11     |
|                                  | hydroxyacyl glutathione hydrolase;<br>glyoxalase 2/HAGH                    | 138760 | NM_005326             | 16p13        |
| <b>Thioesterase</b>              | esterase D/S-formylglutathion<br>hydrolase/ESC (thioesterase)              | 133280 | M13450                | 13q14.11     |
|                                  | aminoacylase 1/ACY1                                                        | 104620 | NM_000666             | 3p21.1       |
|                                  | aminoacylase 2/ACY2/aspartoacylase<br>(Canavan disease)/ASPA               | 271900 | NM_000049             | 17pter-p13   |
|                                  | fatty acid amide hydrolase/FAAH                                            | 602935 | NM_001441             | 1p34-p35     |
| <b>Amidase</b>                   | epoxide hydrolase 1/EPHX1<br>(microsomal)                                  | 132810 | NM_000120             | 1p11-qter    |
|                                  | epoxide hydrolase 2/EPHX2                                                  | 132811 | *****                 | 8p21-p12     |
| <b>Proteases</b>                 | bleomycin hydrolase/BLMH                                                   | 602403 | NM_000386             | 17q11.2      |

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| Transporters | Multidrug resistance protein MDR3/P-glycoprotein 3/PGY3                                      | 602347 | X06181    | 7q21.1        |
|              | Familial intrahepatic cholestasis I, (progressive, Byler disease and benign recurrent) /FIC1 | 602397 | NM_005603 | 18q21         |
|              | Bile salt export pump/BSEP                                                                   | 603201 | NM_003742 | 2q24          |
|              | Microsomal triglyceride transfer protein large subunit/MTP                                   | 157147 | NM_000253 | 4q22-q24      |
|              | Solute carrier family 6, member 6/SLC6A6 (taurine)                                           | 186854 | U16120    | 3p25-q24      |
|              | Solute carrier family 10, member 1/SLC10A1 (taurocholate)                                    | 182396 | NM_003049 | chr. 14       |
|              | Solute carrier family 10, member 2/SLC10A2 (taurocholate)                                    | 601295 | NM_000452 | 13q33         |
|              | Solute carrier family 13, member 2/SLC13A2 (dicarboxylic acids)                              | 604148 | NM_003984 | 17p11.1-q11.1 |
|              | Solute carrier family 19, member 1/SLC19A1 (reduced folate)                                  | 600424 | U19720    | 21q22.3       |
|              | Solute carrier family 21, member 3/SLC21A3 (organic anion)                                   | 602883 | NM_005075 | 12p12         |
|              | Solute carrier family 22, member 1/SLC22A2 (organic cation)                                  | 602607 | NM_003058 | 6q26          |
|              | multidrug resistance protein MDR1                                                            | 171050 | X96395    | 7q21.1        |
|              | multidrug resistance associated protein MRP2/CMOAT                                           | 601107 | NM_000392 | 10q24         |
|              | multidrug resistance protein MDR3/P-glycoprotein 3/PGY3                                      | 602347 | X06181    | 7q21.1        |

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| <b>Canalicular Uptake and Concentration</b> | <b>Bile Salt Synthesis</b> | Bile acid Coenzyme A: amino acid N-acyltransferase (glycine N-choloyltransferase)/BAAT       | 602938 | NM_001701 | 9q22.3        |
|                                             |                            | cytochrome P450, subfamily XLVI (cholesterol 24-hydroxylase)/CYP46                           | 604087 | NM_006668 | 14q32.1       |
|                                             |                            | cytochrome P450, subfamily VIIA (cholesterol 7- $\alpha$ -hydroxylase), polypeptide 1/CYP7A1 | 118455 | M89803    | 8q11-q12      |
|                                             |                            | cytochrome P450, subfamily VIIB (oxysterol 7- $\alpha$ -hydroxylase), polypeptide 1/CYP7B1   | 603711 | AF029403  | 8q21.3        |
|                                             | <b>Bile</b>                | ATPase, Na <sup>+</sup> /K <sup>+</sup> transporting, alpha 1 polypeptide/ATP1A1             | 182310 | NM_000701 | 1p13-p11      |
|                                             |                            | ATPase, Na <sup>+</sup> /K <sup>+</sup> transporting, alpha 1 polypeptide-like/ATP1A1L       | 182360 | NM_001676 | 13q12.1-q12.3 |
|                                             |                            | ATPase, Na <sup>+</sup> /K <sup>+</sup> transporting, alpha 2 polypeptide/ATP1A2             | 182340 | NM_000702 | 1q21-q23      |
|                                             |                            | ATPase, Na <sup>+</sup> /K <sup>+</sup> transporting, beta 1 polypeptide/ATP1B1              | 182330 | NM_001677 | 1q22-q25      |
|                                             |                            | ATPase, Na <sup>+</sup> /K <sup>+</sup> transporting, beta 2 polypeptide/ATP1B2              | 182331 | X16645    | 17p           |
|                                             |                            | ATPase, Na <sup>+</sup> /K <sup>+</sup> transporting, beta 3 polypeptide/ATP1B3              | 601867 | NM_001679 | 3q22-q23      |
|                                             |                            | solute carrier family 4, bicarbonate/chloride anion exchanger, member 1/SLC4A1               | 109270 | NM_000342 | 17q21-q22     |
|                                             |                            | solute carrier family 4, sodium bicarbonate cotransporter, member 4/SLC4A4                   | 603345 | NM_003759 | 4q21          |



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| Concentration  | solute carrier family 4, sodium bicarbonate cotransporter, member 5/SLC4A5 | 603318 | NM_003788 | 4q21         |
|                | Solute carrier family 9, member A2/SLC9A2 (sodium/hydrogen ion)            | 600530 | NM_003048 | 2q11.2       |
|                | Solute carrier family 9, member A3/SLC9A3 (sodium/hydrogen ion)            | 182307 | *****     | 5p15.3       |
|                | chloride channel 5/CLCN5                                                   | 300008 | NM_000084 | Xp11.22      |
|                | chloride channel, calcium activated, family member 1/CLCA1                 | 603906 | NM_001285 | 1p31-p22     |
|                | chloride channel, calcium activated, family member 2/CLCA2                 | 604003 | NM_006536 | *****        |
|                | cystic fibrosis transmembrane conductance regulator/CFTR                   | 602421 | NM_000492 | 7q31.2       |
|                | aquaporin 1/AQP1                                                           | 107776 | NM_000385 | 7p14         |
|                | aquaporin 3/AQP3                                                           | 600170 | NM_004925 | 9p13         |
|                | Cholecystokinin/CCK                                                        | 118440 | L00354    | 3pter-p21    |
| Bile Secretion | Cholecystokinin A receptor/CCKAR                                           | 118444 | L13605    | 4p15.2-p15.1 |
|                | Cholecystokinin B receptor/CCKBR                                           | 118445 | L08112    | 11p15.5-p15  |
|                | Cytoplasmic cysteine conjugate-beta-lyase/glutamine transaminase 1/CCBL1   | 600547 | NM_004059 | Chr.9        |
|                | renal microsomal dipeptidase/DPEP1                                         | 179780 | NM_004413 | 16q24.3      |
|                | alanyl (microsomal) aminopeptidase/aminopeptidase M/ANPEP                  | 151530 | NM_001150 | 15q25-q26    |

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| Excretion            | Hydratases and Lyases | Galectosamine (N-acetyl)-D-sulfate sulfatase (Morquio syndrome)/CALMC | 253000 | NM_000512 | 16q24.3       |
|                      |                       | Iduronate-2-sulfatase (Hunter syndrome)/IDS                           | 309900 | NM_000202 | Xq28          |
|                      |                       | Arylsulfatase A/steroid sulfatase/ARSA                                | 250100 | NM_000487 | 22q13.31-qter |
|                      |                       | Arylsulfatase B/steroid sulfatase/ARSB                                | 253200 | NM_000046 | 5q11-q13      |
|                      |                       | Arylsulfatase C, isozyme s/steroid sulfatase/ARCS1                    | 308100 | NM_000351 | Xp22.32       |
|                      |                       | Arylsulfatase D/steroid sulfatase/ARSD                                | 300002 | *****     | Xp22.3        |
|                      |                       | Arylsulfatase E/steroid sulfatase/ARSE                                | 300180 | NM_000047 | Xp22.3        |
|                      |                       | Arylsulfatase F/steroid sulfatase/ARSF                                | 300003 | NM_004042 | Xp22.3        |
|                      |                       | glucuronidase, beta/GUSB                                              | 253220 | NM_000181 | 7q21.11       |
|                      |                       | renal transport of beta-amino acids/AABT                              | 109660 | *****     | Chr.21        |
| Uptake and Transport |                       | Solute carrier family 3 member 1/SLC3A1 (aa transporter)              | 104614 | *****     | 2p16.3        |
|                      |                       | Solute carrier family 5 member 2/SLC5A5 (Na/glucose transporter)      | 182381 | A56765    | 16p11.2       |
|                      |                       | Solute carrier family 6, member 6/SLC6A6 (taurine)                    | 186854 | U16120    | 3p25-q24      |
|                      |                       | Solute carrier family 7, member 9/SLC7A9 (neutral AA)                 | 604144 | *****     | 19q13.1       |
|                      |                       | Solute carrier family 13, member 2/SLC13A2 (dicarboxylic acids)       | 604148 | NM_003984 | 17p11.1-q11.1 |
|                      |                       |                                                                       |        |           |               |
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| Renal<br>Tubular<br>Uptake and<br>Concentration | Transporters | solute carrier family 17 (sodium phosphate), member 1/SLC17A1                  | 182308 | NM_005074 | 6p23-p21.3 |
|                                                 |              | Solute carrier family 22, member 1/SLC22A2 (organic cation)                    | 602607 | NM_003058 | 6q26       |
|                                                 |              | Solute carrier family 22, member 1-like/SLC22A1L (organic cation)              | 602631 | AF037064  | 11p15.5    |
|                                                 |              | Solute carrier family 22, member 4/SLC22A4 (organic cation)                    | 604190 | NM_003059 | Chr. 5     |
|                                                 |              | Solute carrier family 22, member 5/SLC22A5 (carnitine)                         | 603377 | NM_003060 | 5q33.1     |
|                                                 |              | Solute carrier family 34, member 1/SLC34A1 (sodium phosphate)                  | 182309 | NM_003052 | 5q35       |
|                                                 |              | H <sup>+</sup> -ATPase beta 1 subunit /ATP6B1                                  | 267300 | AH007312  | 2cen-q13   |
|                                                 |              | solute carrier family 4, sodium bicarbonate cotransporter, member 4/SLC4A4     | 603345 | NM_003759 | 4q21       |
|                                                 |              | solute carrier family 4, sodium bicarbonate cotransporter, member 5/SLC4A5     | 603318 | NM_003788 | 4q21       |
|                                                 |              | carbonic anhydrase II/CA2                                                      | 259730 | NM_000067 | 8q22       |
| Acidosis                                        |              | carbonic anhydrase IV/CA4                                                      | 114760 | NM_000717 | 17q23      |
|                                                 |              | carbonic anhydrase XII/CA12                                                    | 603263 | AF051882  | 15q22      |
|                                                 |              | solute carrier family 4, bicarbonate/chloride anion exchanger, member 1/SLC4A1 | 109270 | NM_000342 | 17q21-q22  |
|                                                 |              | Solute carrier family 9, member A1/SLC9A1 (sodium/hydrogen ion)                | 107310 | M81768    | 1p36.1-p35 |
|                                                 |              |                                                                                |        |           |            |

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|                     | Solute carrier family 9, member A2/SLC9A2 (sodium/hydrogen ion)                     | 600530 | NM_003048 | 2q11.2        |
|                     | Solute carrier family 9, member A3/SLC9A3 (sodium/hydrogen ion)                     | 182307 | *****     | 5p15.3        |
| Lithosis            | Solute carrier family 13, member 2/SLC13A2 (dicarboxylic acids)                     | 604148 | NM_003984 | 17p11.1-q11.1 |
| Sodium Tolerance    | 3'(2'), 5'-biphosphate nucleotidase 1/BPNT                                          | 604053 | NM_006085 | *****         |
|                     | chloride channel 5/CLCN5                                                            | 300008 | NM_000084 | Xp11.22       |
|                     | chloride channel Ka, kidney/CLCNKA                                                  | 602024 | NM_004070 | 1p36          |
|                     | chloride channel Kb, kidney/CLCNKB                                                  | 602023 | NM_000085 | 1p36          |
|                     | solute carrier family 12 (sodium/potassium/chloride transporters), member 1/SLC12A1 | 600839 | NM_000338 | 15q15-q21.1   |
|                     | solute carrier family 12 (sodium/potassium/chloride transporters), member 2/SLC12A2 | 600840 | NM_001046 | 5q23.3        |
|                     | solute carrier family 12 (sodium/chloride transporters), member 3/SLC12A3           | 600968 | NM_000339 | 16q13         |
|                     | ATPase, Na+/K+ transporting, alpha 1 polypeptide/ATP1A1                             | 182310 | NM_000701 | 1p13-p11      |
|                     | ATPase, Na+/K+ transporting, alpha 1 polypeptide-like/ATP1A1L                       | 182360 | NM_001676 | 13q12.1-q12.3 |
| Urine Concentration | ATPase, Na+/K+ transporting, alpha 2 polypeptide/ATP1A2                             | 182340 | NM_000702 | 1q21-q23      |

|                      |                                                                                 |        |           |           |
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|                      | ATPase, Na <sup>+</sup> /K <sup>+</sup> transporting, beta 1 polypeptide/ATP1B1 | 182330 | NM_001677 | 1q22-q25  |
|                      | ATPase, Na <sup>+</sup> /K <sup>+</sup> transporting, beta 2 polypeptide/ATP1B2 | 182331 | X16645    | 17p       |
|                      | ATPase, Na <sup>+</sup> /K <sup>+</sup> transporting, beta 3 polypeptide/ATP1B3 | 601867 | NM_001679 | 3q22-q23  |
|                      | arginine vasopressin receptor 2 (nephrogenic diabetes insipidus)/AVPR2          | 304800 | NM_000054 | Xq28      |
|                      | aquaporin 1/AQP1                                                                | 107776 | NM_000385 | 7p14      |
|                      | aquaporin 2/AQP2                                                                | 107777 | NM_000486 | 12q13     |
|                      | aquaporin 3/AQP3                                                                | 600170 | NM_004925 | 9p13      |
|                      | aquaporin 6/AQP6                                                                | 601383 | NM_001652 | 12q13     |
|                      | Superoxide Dismutase 1/SOD1 (soluble)                                           | 147450 | NM_000454 | 21q22.1   |
|                      | Superoxide Dismutase 2/SOD2 (mitochondrial)                                     | 147460 | X65965    | 6q25.3    |
| Superoxide Dismutase | Superoxide Dismutase 3/SOD3 (extracellular)                                     | 185490 | NM_003102 | 4pter-q21 |
|                      | aldehyde dehydrogenase 1/ALDH1 (liver cytosol)                                  | 100640 | AH002598  | 9q21      |
|                      | aldehyde dehydrogenase 2/ALDH2 (liver mitochondria)                             | 100650 | K03001    | 12q24.2   |
|                      | aldehyde dehydrogenase 3/acetaldehyde dehydrogenase 1/ALDH3 (stomach)           | 100660 | M74542    | 17p11.2   |

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|----------------------------------------------------------------|---------------------------------------------------------------------|---------------------------|----------------------------------------------------------------------------------------------------------|--------|---------------|----------|
| Metabolism<br>of Reactive<br>Oxygen and<br>Nitrogen<br>Species | Protection<br>from<br>Reactive<br>Oxygen and<br>Nitrogen<br>Species | Aldehyde<br>Dehydrogenase | 5/acetalddehyde<br>aldehyde dehydrogenase 5, member<br>A1/succinic semialdehyde<br>dehydrogenase/ALDH5A1 | 100670 | NM_00069<br>2 | 9p13     |
|                                                                |                                                                     |                           | 6/acetalddehyde<br>aldehyde dehydrogenase 6, member<br>A1/succinic semialdehyde<br>dehydrogenase/ALDH6A1 | 271980 | NM_00108<br>0 | 6p22     |
|                                                                |                                                                     |                           | 7/acetalddehyde<br>aldehyde dehydrogenase 7, member<br>A1/succinic semialdehyde<br>dehydrogenase/ALDH7A1 | 600463 | NM_00069<br>3 | 15q26    |
|                                                                |                                                                     |                           | 8/acetalddehyde<br>aldehyde dehydrogenase 8/ALDH8                                                        | 600466 | NM_00069<br>4 | 11q13    |
|                                                                |                                                                     |                           | 9/acetalddehyde<br>aldehyde dehydrogenase 9/g-<br>aminobutyraldehyde<br>dehydrogenase/ALDH9              | 601917 | NM_00069<br>5 | chr. 11  |
|                                                                |                                                                     |                           | 10/acetalddehyde<br>aldehyde dehydrogenase 10/ALDH10                                                     | 602733 | NM_00069<br>6 | 1q22-q23 |
|                                                                |                                                                     |                           | 11/acetalddehyde<br>aldehyde dehydrogenase 11/ALDH11                                                     | 270200 | NM_00038<br>2 | 17p11.2  |
|                                                                |                                                                     |                           | 12/acetalddehyde<br>aldehyde dehydrogenase 12/ALDH12                                                     | 602841 | NM_00115<br>9 | 2q33     |
|                                                                |                                                                     |                           | 13/acetalddehyde<br>aldehyde dehydrogenase 13/ALDH13                                                     | 230450 | NM_00149<br>8 | 6p12     |
|                                                                |                                                                     |                           | 14/acetalddehyde<br>aldehyde dehydrogenase 14/ALDH14                                                     | 601176 | NM_00206<br>1 | 1p22.1   |
| Glutathione                                                    |                                                                     | Glutathione               | glutathione synthetase/GSS                                                                               | 601002 | NM_00017<br>8 | 20q11.2  |
|                                                                |                                                                     |                           | glutathione peroxidase/GPX1                                                                              | 138320 | M21304        | 3p21.3   |
|                                                                |                                                                     |                           | glutathione peroxidase GPX2                                                                              | 138319 | X68314        | 14q24.1  |

|                  |                                                                            |        |           |             |
|------------------|----------------------------------------------------------------------------|--------|-----------|-------------|
|                  | glutathione peroxidase GPX3                                                | 138321 | X58295    | 5q32-q33.1  |
|                  | glutathione peroxidase GPX4                                                | 138322 | X71973    | 19p13.3     |
|                  | glutathione peroxidase GPX5                                                | 603435 | AJ005277  | *****       |
|                  | glutathione reductase                                                      | 138300 | X15722    | 8p21.1      |
| Metallothioneins | metallothionein 1A/MT1A                                                    | 156350 | NM_005953 | 16q13       |
|                  | metallothionein 1B                                                         | 56349  | AH001510  | 16q13       |
|                  | metallothionein 1E                                                         | 156351 | M10942    | 16q13       |
|                  | metallothionein 1F                                                         | 156352 | M10943    | 16q13       |
|                  | metallothionein 1G                                                         | 156353 | J03910    | 16q13       |
|                  | metallothionein 2A/MT2A                                                    | 156360 | NM_005953 | 16q13       |
|                  | metallothionein 3                                                          | 139255 | NM_005954 | 16q13       |
|                  | glucose-6-phosphate dehydrogenase/G6PD (mitochondrial)                     | 305900 | NM_000402 | Xq28        |
| Miscellaneous    | 8-oxoguanine DNA glycosylase/CGGI                                          | 601982 | NM_002542 | 3p26.2      |
|                  | Peptide methionine sulfoxide reductase/MSRA                                | 601250 | *****     | *****       |
|                  | succinate dehydrogenase complex, subunit C, integral membrane protein/SDHC | 602413 | NM_003001 | 1q21        |
|                  | phospholipase A2 group IB/PLA2G1B                                          | 172410 | NM_000928 | 12q23-q24.1 |
|                  | lipoprotein, Lp(a)/LPA                                                     | 152200 | NM_005577 | 6q27        |
|                  | Catalase/CAT                                                               | 115500 | NM_001752 | 11p13       |

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|                                    | thioredoxin-dependent peroxide reductase/TDPX1   | 600538 | NM_005809 | 13q12        |
| <b>IgE Production</b>              | interleukin 4 receptor/IL4R                      | 147781 | X52425    | 6p12.1-p11.2 |
|                                    | interferon gamma/IFNG                            | 147570 | L07633    | 12q14        |
| <b>Mast Cell Proliferation</b>     | mast cell growth factor/MGF                      | 184745 | NM_003994 | 12q22        |
|                                    | interleukin 9 receptor/IL9R                      | 300007 | M84747    | Xq28         |
|                                    | interleukin 3 receptor/IL3R)                     | 308385 | M74782    | Xp22.3       |
| <b>Degranulation of Mast Cells</b> | mast cell IgE receptor alpha polypeptide/FCER1A  | 147140 | *****     | 1q23         |
|                                    | mast cell IgE receptor beta polypeptide/FCER1B   | 147138 | NM_000139 | 11q13        |
|                                    | mast cell IgE receptor beta polypeptide/FCER1G   | 147139 | NM_004106 | 1q23         |
|                                    | SH2-containing inositol 5-phosphatase/SHIP       | 601582 | U57650    | 2q36-q37     |
|                                    | secretory granule proteoglycan peptide core/PRG1 | 177040 | J03223    | 10q22.1      |
| <b>Histamine</b>                   | Histidine Decarboxylase                          | 142704 | M60445    | 15q21-q22    |
|                                    | Histamine receptor H1                            | 600167 | AF026261  | 3p21-p14     |
|                                    | Histamine receptor H2                            | 142703 | M64799    | *****        |
|                                    | Histamine N-methyltransferase                    | *****  | D16224    | chr. 2       |
|                                    | Amine oxidase (copper-containing) 2/AOC2         | 602268 | D88213    | 17q21        |
|                                    | Amine oxidase (copper-containing) 3/AOC3         | 603735 | AF054985  | 17q21        |
|                                    | aromatic L-Amino Acid Decarboxylase/AADC         | 107930 | M76180    | 7p11         |



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| Serotonin | tryptophan hydroxylase/TPH                            | 191060 | X52836    | 11p15.3-p14  |
|           | 14-3-3 protein ETA                                    | 113508 | X78138    | 22q12        |
|           | 14-3-3 protein ZETA                                   | 601288 | M86400    | 2p25.2-p25.1 |
|           | 14-3-3 protein BETA                                   | 601289 | X57346    | 20q13.1      |
|           | 14-3-3 protein SIGMA                                  | 601290 | X57348    | *****        |
|           | serotonin 5-HT receptors 5-HT1A, G<br>protein-coupled | 109760 | X57829    | 5q11.2-q13   |
|           | serotonin 5-HT receptors 5-HT1B, G<br>protein-coupled | 182131 | M81590    | 6q13         |
|           | serotonin 5-HT receptors 5-HT1C, G<br>protein-coupled | 312861 | U49516    | Xq24         |
|           | serotonin 5-HT receptors 5-HT1D, G<br>protein-coupled | 182133 | M81590    | 1p36.3-p34.3 |
|           | serotonin 5-HT receptors 5-HT1E, G<br>protein-coupled | 182132 | M91467    | 6q14-q15     |
|           | serotonin 5-HT receptors 5-HT1F, G<br>protein-coupled | 182134 | L05597    | 3p12         |
|           | serotonin 5-HT receptors 5-HT2A, G<br>protein-coupled | 182135 | D87030    | 13q14-q21    |
|           | serotonin 5-HT receptors 5-HT2B, G<br>protein-coupled | 601122 | X77307    | 2q36.3-q37.1 |
|           | serotonin 5-HT receptors 5-HT2C, G<br>protein-coupled | 312861 | U49516    | Xq24         |
|           | serotonin transporter                                 | 182138 | X70697    | 17q11.1-q12  |
|           | monoamine oxidase A/ MAOA                             | 309850 | M69226    | Xp11.23      |
|           | monoamine oxidase B MAOB                              | 309860 | M69177    | Xp11.23      |
|           | serotonin N-Acetyltransferase/SNAT                    | 600950 | U40347    | 17q25        |
|           | tryptophan 2,3-dioxygenase/TDO2                       | 191070 | NM_005651 | 4q31-q32     |

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| <b>Neutrophil and Eosinophil Chemotaxis</b>                                                   | eotaxin precursor/small inducible cytokine, family A, member     | 601156 | U46572    | 7q21.1-q21.2 |
|                                                                                               | monocyte-derived-neutrophil chemotactic factor/interleukin 8/IL8 | 146930 | M26383    | 4q12-q13     |
| <b>Proteases</b>                                                                              | tryptase alpha/TPS1                                              | 191080 | NM_003293 | Chr.16       |
|                                                                                               | tryptase beta/TPS2                                               | 191081 | NM_003294 | Chr.16       |
|                                                                                               | chymase 1, mast cell/CMA1                                        | 118938 | NM_001836 | 14q11.2      |
| <b>Release of Membrane Lipids</b><br>(common to PAF, leukotriene, and prostaglandin pathways) | phospholipase A2 group IIA/PLA2G2A                               | 172411 | NM_000300 | 1p35         |
|                                                                                               | phospholipase A2 group IB/PLA2G1B                                | 172410 | NM_000928 | 12q23-q24.1  |
|                                                                                               | phospholipase A2 group X/PLA2G10                                 | 603603 | *****     | 16p13.1-p12  |
|                                                                                               | phospholipase A2 group IVA/PLA2G4A                               | 600522 | U08374    | 1q25         |
|                                                                                               | phospholipase A2 group VI/PLA2G6                                 | 603604 | AF064594  | 22q13.1      |
|                                                                                               | phospholipase A2 group IVC/PLA2G4C                               | 603602 | *****     | chr. 19      |
|                                                                                               | phospholipase A2 group V/PLA2G5                                  | 601192 | NM_000929 | 1p36-p34     |
|                                                                                               | phospholipase C beta 3                                           | 600230 | U26425    | 11q13        |
|                                                                                               | lysosomal acid lipase                                            | 278000 | NM_000235 | 10q24-q25    |
|                                                                                               | CDP-choline:alkylacetylgllycerol cholinephosphotransferase       | *****  | *****     | *****        |
| <b>Platelet Activation</b>                                                                    | platelet activating factor receptor/PTAFR                        | 173393 | M88177    | 1p35-p34.3   |
|                                                                                               | platelet activating factor acetylhydrolase 1/PAFAH1              | 601690 | NM_005084 | 6p21.2-p12   |

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|-------------------------------------------------|------------------------------------------------------------------|--------|-----------|-------------------|
| <b>Platelet<br/>Activating<br/>Factor (PAF)</b> | platelet activating factor<br>acetylhydrolase, isoform 1B, alpha | 601545 | NM_000430 | 17p13.3           |
|                                                 | platelet activating factor<br>acetylhydrolase, isoform 1B, beta  | 602508 | NM_002572 | 11q23             |
|                                                 | platelet activating factor<br>acetylhydrolase, isoform 1B, gamma | 603074 | NM_002573 | 19q13.1           |
|                                                 | platelet activating factor<br>acetylhydrolase 2/PAFAH2           | 602344 | NM_000437 | *****             |
| <b>Leukotriene</b>                              | arachidonate 5-lipoxygenase/ALOX5                                | 152390 | NM_000698 | Chr.10            |
|                                                 | arachidonate 5-lipoxygenase-<br>activating protein/FLAP/ALOX5AP  | 603700 | NM_001629 | 13q12             |
|                                                 | leukotriene A4 hydrolase/LTA4H                                   | 151570 | NM_000895 | 12q22             |
|                                                 | leukotriene C4 synthase/LTC4S                                    | 246530 | NM_000897 | 5q35              |
|                                                 | Gamma-glutamyltranspeptidase<br>1/GGT1                           | 231950 | J04131    | 22q11.1-<br>q11.2 |
|                                                 | Gamma-glutamyltranspeptidase<br>2/GGT2                           | 137181 | AH002728  | 22q11.1           |
|                                                 | Gamma-glutamyltransferase-like<br>activity 1/GGTLA1              | 137168 | NM_004121 | *****             |
|                                                 | renal microsomal dipeptidase/DPEP1                               | 179780 | NM_004413 | 16q24.3           |
|                                                 | cysteinyl leukotriene receptor<br>1/CYSLT1                       | 300201 | NM_006669 | Xq13-q21          |
|                                                 | leukotriene b4 receptor (chemokine<br>receptor-like 1)/LTB4R     | 601531 | NM_000752 | 14q11.2-<br>q12   |

|                |                                                       |        |           |              |
|----------------|-------------------------------------------------------|--------|-----------|--------------|
| Prostaglandins | prostaglandin endoperoxide synthetase 1/COX1/PTGS1    | 176805 | AH001520  | 9q32-q33.3   |
|                | prostaglandin endoperoxide synthetase 2/COX2/PTGS2    | 600262 | NM_000963 | 1q25.2-q25.3 |
|                | thromboxane A synthase 1/TBXAS1                       | 274180 | SEG_D3461 | 7q34         |
|                | prostaglandin D2 synthase                             | 602598 | M61900    | *****        |
|                | prostaglandin I2 synthase/prostacyclin synthase/PTGIS | 601699 | SEG_D8339 | 20q13        |
|                | prostaglandin E receptor 1, EP1 subtype/PTGER1        | 176802 | NM_000955 | 19p13.1      |
|                | prostaglandin E receptor 2, EP2 subtype/PTGER2        | 176804 | *****     | 5p13.1       |
|                | prostaglandin E receptor 3, EP3 subtype/PTGER3        | 176806 | NM_000957 | 1p31.2       |
|                | prostaglandin E receptor 4, EP4 subtype/PTGER4        | 601586 | NM_000958 | 5p13.1       |
|                | prostaglandin F receptor/PTGFR                        | 600563 | L24470    | 1p31.1       |
|                | prostaglandin F2 receptor negative regulator/PTGFRN   | 601204 | U26664    | 1p13.1-q21.3 |
|                | prostaglandin I2 receptor/PTGIR/prostacyclin receptor | 600022 | SEG_HUM1  | 19q13.3      |
|                | 15-hydroxyprostaglandin dehydrogenase/HPGD            | 601688 | NM_000860 | 4q34-q35     |
|                | aldo-keto reductase family 1, member C2/AKR1C2        | 600450 | NM_001353 | 10p15-p14    |
|                | myeloperoxidase/MPO                                   | 254600 | J02694    | 17q23.1      |
|                | eosinophil peroxidase/EPX                             | 131399 | NM_000502 | *****        |

Mast Cell  
and T-Cell  
Response

|                                 |                                         |        |           |          |
|---------------------------------|-----------------------------------------|--------|-----------|----------|
| <b>Drug<br/>Activation</b>      | calreticulin/CALR                       | 109091 | CALR      | 19p13.2  |
|                                 | calnexin/CANX                           | 114217 | L18887    | 5q35     |
|                                 | ceruloplasmin (ferroxidase)/CP          | 117700 | NM_000096 | 3q21-q24 |
| <b>Antigen<br/>Presentation</b> | MHC class II transactivator/MHC2TA      | 600005 | NM_000246 | 16p13    |
|                                 | MHC class II HLA DR-alpha chain/HLA-DRA | 142860 | X83114    | 6p21.3   |
|                                 | MHC class II HLA DR-beta chain/HLA-DRB  | 142857 | M11161    | 6p21.3   |
|                                 | MHC class II HLA DP-alpha chain/HLA-DPA | 142880 | M23905    | 6p21.3   |
|                                 | MHC class II HLA DP-beta chain/HLA-DPB  | 142858 | AH002893  | 6p21.3   |
|                                 | MHC class II HLA DM-alpha chain/HLA-DMA | 142855 | NM_006120 | 6p21.3   |
|                                 | MHC class II HLA DM-beta chain/HLA-DMB  | 142856 | NM_002118 | 6p21.3   |
|                                 | MHC class II HLA DQ-alpha chain/HLA-DQA | 146880 | M11124    | 6p21.3   |
|                                 | MHC class II HLA DQ-beta chain/HLA-DQB  | *****  | M24364    | 6p21.3   |
|                                 | MHC class II HLA DN-alpha chain/HLA-DNA | 142930 | X02882    | 6p21.3   |
|                                 | MHC class II HLA DO-beta chain/HLA-DOB  | 600629 | NM_002120 | 6p21.3   |
|                                 | MHC class II antigen gamma chain/CD74   | 142790 | K01144    | 5q32     |

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|                        | antigen peptide transporter 1/MHC 1/TAP1                                         | 170260 | NM_000593 | 6p21.3   |
|                        | antigen peptide transporter 2/MHC 2/TAP2                                         | 170261 | NM_000544 | 6p21.3   |
| <b>T-Cell Receptor</b> | T-cell antigen receptor, alpha subunit/TCRA                                      | 186880 | Z24457    | 14q11.2  |
|                        | T-cell antigen receptor, beta subunit/TCRB                                       | 186930 | AF011643  | 7q35     |
|                        | T-cell antigen receptor, gamma subunit/TCRG                                      | 186970 | M17325    | 7p15-p14 |
|                        | T-cell antigen receptor, delta subunit/TCRD                                      | 186810 | L36384    | 14q11.2  |
|                        | thymocyte antigen receptor complex CD3G, gamma polypeptide (TiT3 complex)/CD3G   | 186740 | NM_000073 | 11q23    |
|                        | thymocyte antigen receptor complex CD3D, delta polypeptide (TiT3 complex)/CD3D   | 186790 | NM_000073 | 11q23    |
|                        | thymocyte antigen receptor complex CD3E, epsilon polypeptide (TiT3 complex)/CD3E | 186830 | NM_000073 | 11q23    |
|                        | thymocyte antigen receptor complex CD3Z, zeta polypeptide (TiT3 complex)/CD3Z    | 186780 | NM_000073 | 1q22-q23 |
|                        | ataxia telangiectasia mutated (includes complementation groups A, C and D)/ATM   | 208900 | NM_000051 | 11q22.3  |
|                        | recombination activating gene 1/RAG1                                             | 179615 | NM_000448 | 11p13    |

| T-Cell<br>Receptor<br>Rearrangement | recombination activating gene                                                      |     | 179616 | M94633    | 11p13         |
|-------------------------------------|------------------------------------------------------------------------------------|-----|--------|-----------|---------------|
|                                     | α/β                                                                                | γ/δ |        |           |               |
| T-Cell<br>Receptor<br>Rearrangement | interleukin 7 receptor/IL7R                                                        |     | 146661 | NM_002185 | 5p13          |
|                                     | v-myb avian myeloblastosis viral oncogene homolog/MYB                              |     | 189990 | NM_005375 | 6q22          |
|                                     | core binding factor, alpha 1 subunit/CBFA1                                         |     | 600211 | AH005498  | 6p21          |
|                                     | core-binding factor, beta subunit/PEBP2B/CBFB                                      |     | 121360 | L20298    | 16q22         |
|                                     | ligase I, DNA, ATP-dependent/LIG1                                                  |     | 126391 | NM_000234 | 19q13.2-q13.3 |
|                                     | ligase IV, DNA, ATP-dependent/LIG4                                                 |     | 601837 | NM_002312 | 13q22-q34     |
|                                     | X-ray repair, complementing defect in Chinese hamster/Ku antigen, 80 kD/KU80/XRCC5 |     | 194364 | *****     | 2q35          |
|                                     | thyroid autoantigen, 70 kD/KU70/G22P1                                              |     | 152690 | NM_001469 | 22q11-q13     |
|                                     | T-cell antigen T4/CD4                                                              |     | 186940 | X87579    | 12pter-p12    |
|                                     | T-cell antigen CD8, alpha polypeptide (p32)/CD8A                                   |     | 186910 | NM_001768 | 2p12          |
|                                     | T-cell antigen CD8, beta polypeptide/CD8B                                          |     | 186730 | AH003859  | 2p12          |
|                                     | T-cell antigen CD28 (Tp44)/CD28                                                    |     | 186760 | NM_006139 | 2q33-q34      |
|                                     | cytotoxic T-lymphocyte-associated 4/CTLA4                                          |     | 123890 | L15006    | 2q33          |

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|-----------------------------------------------------------------|--------|-----------|---------------|
| CD80 antigen (CD28 antigen ligand 1, B7-1 antigen)/CD80         | 112203 | NM_005191 | 3q21          |
| CD86 antigen (CD28 antigen ligand 2, B7-2 antigen)/CD86         | 601020 | NM_006889 | 3q21          |
| T cell receptor-associated protein tyrosine kinase ZAP-70/ZAP70 | 176947 | S69911    | 2q12          |
| leukocyte common antigen CD45                                   | 151460 | M23492    | 1q31-q32      |
| nuclear factor of activated T-cells, cytoplasmic 1/NFATC1       | 600489 | NM_006162 | 18q23         |
| nuclear factor of activated T-cells, cytoplasmic 2/NFATC2       | 600490 | *****     | 20q13.2-q13.3 |
| nuclear factor of activated T-cells, cytoplasmic 3/NFATC3       | 602698 | L41066    | 16q13-q24     |
| nuclear factor of activated T-cells, cytoplasmic 4/NFATC4       | 602699 | L41067    | *****         |
| interleukin 2 receptor alpha/IL2RA                              | 147730 | X01057    | 10p15-p14     |
| interleukin 2 receptor beta/IL2RB                               | 146710 | M26062    | 22q11.2-q13   |
| interleukin 2 receptor gamma/IL2RG                              | 308380 | D11086    | Xq13          |
| interleukin 6 receptor/IL6R                                     | 147880 | X12830    | 1q21          |
| interleukin 9 receptor/IL9R                                     | 300007 | M84747    | Xq28          |
| interleukin receptor 13 alpha/IL13RA1                           | 300119 | S80963    | Chr.X         |
| interleukin receptor 13 alpha2/IL13RA2                          | 300130 | X95302    | Xq24          |
| interleukin 15 receptor alpha/IL15RA                            | 601070 | U31628    | 10p15-p14     |
| transforming growth factor/TGFB1                                | 190180 | M60315    | 19q13.1-q13   |
| transforming growth factor/TGFB2                                | 190220 | M19154    | 1q41          |
| transforming growth factor/TGFB3                                | 190230 | X14149    | 14q24         |
| tumor necrosis factor beta/TNFB/lymp                            | 153440 | NM_000595 | 6p21.3        |

### T-Cell Expansion

**Immune  
Response**  
(additional  
genes in  
Immunology)



|                                                                                                               |        |               |          |
|---------------------------------------------------------------------------------------------------------------|--------|---------------|----------|
| tumor necrosis factor ligand<br>superfamily, member 6/TNFSF6                                                  | 134638 | NM_00063<br>9 | 1q23     |
| tumor necrosis factor receptor<br>superfamily, member 6/TNFRSF6                                               | 134637 | NM_00004<br>3 | 10q24.1  |
| caspase 10, apoptosis-related cysteine<br>protease/CASP10                                                     | 601762 | NM_00123<br>0 | 2q33-q34 |
| B-cell antigen CD20/B-lymphocyte<br>differentiation antigen B1/CD20                                           | 112210 | AH003353      | 11q13    |
| B-cell antigen CD72/CD72                                                                                      | 107272 | NM_00178<br>2 | 9p       |
| natural resistance-associated<br>macrophage protein<br>1/NRAMP1/solute carrier family 11,<br>member 1/SLC11A2 | 600266 | AH002806      | 2q35     |
| natural resistance-associated<br>macrophage protein<br>2/NRAMP2/solute carrier family 11,<br>member 2/SLC11A2 | 600523 | AB015355      | 12q13    |
| T-lymphocyte antigen CDW52<br>(CAMPATH-1 antigen)/CDW52                                                       | 114280 | NM_00180<br>3 | *****    |
| B-cell antigen CD22/CD22                                                                                      | 107266 | NM_00177<br>1 | 19q13.1  |
| B-cell antigen CD24/CD24                                                                                      | 600074 | X69397        | 6q21     |
| leukocyte antigen CD156/disintegrin<br>and metalloprotease domain<br>8/ADAM8/CD156                            | 602267 | NM_00110<br>9 | 10q26.3  |
| platelet antigen CD151/platelet-<br>endothelial cell tetraspan antigen<br>3/PETA3/CD151                       | 602243 | NM_00435<br>7 | 11p15.5  |

## Receptors

|                                    |                                                                |        |           |              |
|------------------------------------|----------------------------------------------------------------|--------|-----------|--------------|
|                                    | IIA for Fc fragment of IgG/FCGR2A/CD32                         | 146790 | NM_004001 | 1q21-q23     |
|                                    | activated leucocyte cell adhesion molecule/CD6 ligand/ALCAM    | 601662 | NM_001627 | 3q13.1-q13.2 |
|                                    | lymphocyte antigen CD79A/immunoglobulin-associated alpha/CD79A | 112205 | NM_001783 | 19q13.2      |
|                                    | lymphocyte antigen CD79B/immunoglobulin-associated beta/CD79B  | 147245 | L27587    | 17q23        |
| <b>Signalling</b>                  | regulator of G-protein signalling 1/RGS1                       | 600323 | NM_002922 | 1q31         |
| <b>Immunoglobulin Light Chains</b> | immunoglobulin K light chain constant region locus/IGKC        | 147200 | *****     | 2p12         |
|                                    | immunoglobulin K light chain variable region locus/IGKV        | 146980 | K01322    | 2p12         |
|                                    | immunoglobulin K light chain joining region locus/IGKJ         | 146970 | *****     | 2p12         |
|                                    | immunoglobulin L light chain constant region locus/IGLC1       | 147220 | NM_006146 | 22q11.2      |
|                                    | immunoglobulin L light chain joining region locus/IGLJ         | 147230 | NM_006146 | 22q11.2      |
|                                    | immunoglobulin L light chain variable region locus/IGLJ        | 147240 | NM_006146 | 22q11.2      |
|                                    | immunoglobulin A heavy chain constant region locus 1/IGHA1     | 146900 | *****     | 14q32.33     |
|                                    | immunoglobulin A heavy chain constant region locus 2/IGHA2     | 147000 | *****     | 14q32.33     |

|                             |                                                            |        |           |           |
|-----------------------------|------------------------------------------------------------|--------|-----------|-----------|
| Immunoglobulin Heavy Chains | immunoglobulin D heavy chain constant region locus/IGHD    | 147170 | *****     | 14q32.33  |
|                             | immunoglobulin E heavy chain constant region locus/IGHE    | 147180 | *****     | 14q32.33  |
|                             | immunoglobulin G heavy chain constant region locus 1/IGHG1 | 147100 | *****     | 14q32.33  |
|                             | immunoglobulin G heavy chain constant region locus 2/IGHG2 | 147110 | *****     | 14q32.33  |
|                             | immunoglobulin G heavy chain constant region locus 3/IGHG3 | 147120 | *****     | 14q32.33  |
|                             | immunoglobulin G heavy chain constant region locus 4/IGHG4 | 147130 | *****     | 14q32.33  |
|                             | immunoglobulin M heavy chain constant region locus/IGHM    | 147020 | *****     | 14q32.33  |
|                             | immunoglobulin heavy chain variable region locus 1/IGHV1   | 147070 | X92279    | 14q32.33  |
|                             | immunoglobulin heavy chain variable region locus 2/IGHV2   | 600949 | *****     | 16p11     |
|                             | immunoglobulin heavy chain diversity region locus 1/IGHDY1 | 146910 | X97051    | 14q32.33  |
|                             | immunoglobulin heavy chain diversity region locus 2/IGHDY2 | 146990 | L25544    | 15q11-q12 |
|                             | immunoglobulin heavy chain joining region locus/IGHJ       | 147010 | *****     | 14q32.33  |
|                             | recombination activating gene 1/RAG1                       | 179615 | NM_000448 | 11p13     |
|                             | recombination activating gene 2/RAG2                       | 179616 | M94633    | 11p13     |

| B-Cell<br>Response | Immunoglobulin Gene<br>Rearrangement                                               | 147183 | L07872    | 9p13-p12      |
|--------------------|------------------------------------------------------------------------------------|--------|-----------|---------------|
|                    |                                                                                    |        |           |               |
|                    | immunoglobulin kappa J region recombination signal binding protein/RBPJK/IGKJRB1   | 147183 | L07872    | 9p13-p12      |
|                    | Bruton agammaglobulinemia tyrosine kinase/BTK                                      | 300300 | NM_000061 | Xq21.3-q22    |
|                    | interleukin 7 receptor/IL7R                                                        | 146661 | NM_002185 | 5p13          |
|                    | interferon-gamma receptor 1/IFNGR1                                                 | 107470 | NM_000416 | 6q23-q24      |
|                    | interferon-gamma receptor 2/IFNGR2                                                 | 147569 | NM_005534 | 21q22.1-q22.2 |
|                    | interleukin 4 receptor precursor/IL4R                                              | 147781 | NM_000418 | 16p12.1-p11.2 |
|                    | interleukin 4 receptor precursor/IL4R                                              | 147781 | NM_000418 | 16p12.1-p11.2 |
|                    | ligase I, DNA, ATP-dependent/LIG1                                                  | 126391 | NM_000234 | 19q13.2-q13.3 |
|                    | ligase IV, DNA, ATP-dependent/LIG4                                                 | 601837 | NM_002312 | 13q22-q34     |
|                    | X-ray repair, complementing defect in Chinese hamster/Ku antigen, 80 kD/KU80/XRCC5 | 194364 | *****     | 2q35          |
|                    | thyroid autoantigen, 70 kD/KU70/G22P1                                              | 152690 | NM_001469 | 22q11-q13     |
|                    | nuclear factor kappa-B DNA binding subunit 1/NFKB1                                 | 164011 | M58603    | 4q23-q24      |
|                    | nuclear factor kappa-B DNA binding subunit 2/NFKB2                                 | 164012 | NM_002502 | 10q24         |

|                                   |                                                                                      |        |           |               |
|-----------------------------------|--------------------------------------------------------------------------------------|--------|-----------|---------------|
| Immunoglobulin Gene Transcription | nuclear factor kappa-B subunit 3/NFKB3                                               | 164014 | Z22949    | 11q12-q13     |
|                                   | nuclear factor of kappa light chain gene enhancer in B cells, inhibitor alpha/NFKBIA | 164008 | *****     | 14q13         |
|                                   | nuclear factor of kappa light chain gene enhancer in B cells, inhibitor beta/NFKBIB  | 603258 | NM_002503 | 8p11.2        |
|                                   | YY1 transcription factor/YY1                                                         | 600013 | NM_003403 | 14q           |
|                                   | immunoglobulin transcription factor 1/ITF1/transcription factor 3/TCF3               | 147141 | *****     | 19p13.3       |
|                                   | immunoglobulin transcription factor 2/ITF2/transcription factor 4/TCF4               | 602272 | NM_003199 | 18q21.1       |
|                                   | immunoglobulin mu binding protein 2/IGHMBP2                                          | 600502 | NM_002180 | 11q13.2-q13.4 |
|                                   | transcription factor binding to IGHM enhancer 3/TFE3                                 | 314310 | NM_006521 | Xp11.22       |
|                                   | homeobox protein OCT1/POU domain transcription factor 2, class 1/POU2F1              | 164175 | NM_002697 | 1q22-q23      |
|                                   | homeobox protein OCT2/POU domain transcription factor 2, class 2/POU2F2              | 164176 | M22596    | Chr.19        |
|                                   | POU domain, class 2, associating factor 1/POU2AF1                                    | 601206 | NM_006235 | 11q23.1       |
|                                   | inhibitor of DNA binding 1, dominant negative helix-loop-helix protein/ID1           | 600349 | NM_002165 | 20q11.1       |
|                                   | inhibitor of DNA binding 2, dominant negative helix-loop-helix protein/ID2           | 600386 | NM_002166 | 2p25          |

|                                   |                                                                                               |        |           |               |
|-----------------------------------|-----------------------------------------------------------------------------------------------|--------|-----------|---------------|
| Immunoglobulin Isootype Switching | B-cell antigen CD40/tumor necrosis factor receptor superfamily, member 5/CD40/TNFRSF5         | 109535 | NM_001250 | 20q12-q13.2   |
|                                   | paired box gene 5/B-cell lineage-specific activator protein/BSAP/PAX5                         | 167414 | *****     | 9p13          |
|                                   | lymphocyte function-associated antigen, type 3/LFA3/LEU7/CD58                                 | 153420 | NM_001779 | 1p13          |
|                                   | interleukin 10 receptor, alpha/IL10RA                                                         | 146933 | NM_001558 | 11q23.3       |
|                                   | lymphocyte antigen CD45/protein tyrosine phosphatase, receptor type, c polypeptide/PTPRC/CD45 | 151460 | NM_002838 | 1q31-q32      |
|                                   | prostaglandin E receptor 1, EP1 subtype/PTGER1                                                | 176802 | NM_000955 | 19p13.1       |
|                                   | prostaglandin E receptor 2, EP2 subtype/PTGER2                                                | 176804 | *****     | 5p13.1        |
|                                   | prostaglandin E receptor 3, EP3 subtype/PTGER3                                                | 176806 | NM_000957 | 1p31.2        |
|                                   | prostaglandin E receptor 4, EP4 subtype/PTGER4                                                | 601586 | NM_000958 | 5p13.1        |
|                                   | interleukin 13 receptor, alpha 1/IL13RA1                                                      | 300119 | NM_001560 | Chr.X         |
|                                   | interleukin receptor 13 alpha2/IL13A2                                                         | 300130 | X95302    | Xq24          |
|                                   | interferon-gamma receptor 1/IFNGR1                                                            | 107470 | NM_000416 | 6q23-q24      |
|                                   | interferon-gamma receptor 2/IFNGR2                                                            | 147569 | NM_005534 | 21q22.1-q22.2 |
|                                   | interleukin 5 receptor alpha/IL5RA                                                            | 147851 | M96652    | 3p26-p24:     |

|                                                                                                          |        |               |                   |
|----------------------------------------------------------------------------------------------------------|--------|---------------|-------------------|
| transforming growth factor, beta<br>receptor I (activin A receptor type II-<br>like kinase, 53kD)/TGFBRI | 190181 | NM_00461<br>2 | 9q33-q34          |
| transforming growth factor, beta<br>receptor II (70-80kD)/TGFBRII                                        | 190182 | NM_00324<br>2 | 3p22              |
| transforming growth factor, beta<br>receptor III (betaglycan,<br>300kD)/TGFBRIII                         | 600742 | NM_00324<br>3 | 1p33-p32          |
| X-ray repair, complementing defect in<br>Chinese hamster/Ku antigen, 80<br>kD/KU80/XRCC5                 | 194364 | *****         | 2q35              |
| thyroid autoantigen, 70<br>kD/KU70/G22P1                                                                 | 152690 | NM_00146<br>9 | 22q11-q13         |
| granulocyte-macrophage colony<br>stimulating factor 2/CSF2                                               | 138960 | NM_00075<br>8 | 5q31.1            |
| macrophage-specific colony-<br>stimulating factor/CSF1                                                   | 120420 | AH005300      | 1p21-p13          |
| granulocyte colony stimulating factor<br>3/CSF3                                                          | 138970 | NM_00075<br>9 | 17q11.2-<br>q12   |
| colony stimulating factor 1<br>receptor/CSFR1                                                            | 164770 | U63963        | 5q33.2-<br>q33.3  |
| granulocyte-macrophage colony<br>stimulating factor 2 receptor, alpha,<br>low-affinity/CSF2RA            | 306250 | NM_00614<br>0 | Xp22.32           |
| granulocyte-macrophage colony<br>stimulating factor 2 receptor,<br>beta/CSF2RB                           | 138981 | U18373        | 22q12.2-<br>q13.1 |
| granulocyte-macrophage colony<br>stimulating factor 2 receptor, alpha, Y<br>chromosomal/CSF2RY           | 425000 | *****         | Yp11              |

|                            |                                                                                |                                                                                              |        |               |                   |
|----------------------------|--------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------|--------|---------------|-------------------|
| Myeloid<br>Differentiation | Granulocyte,<br>Macrophage,<br>Erythrocyte,<br>and Platelet<br>Differentiation | Flt3 ligand/FMS-related tyrosine<br>kinase 3 ligand/FLT3LG                                   | 600007 | U03858        | 19q13.3           |
|                            |                                                                                | STAT induced STAT inhibitor 3/SSI-<br>3                                                      | 604176 | NM_00395<br>5 | *****             |
|                            |                                                                                | erythropoietin/EPO                                                                           | 133170 | NM_00079<br>9 | 7q21              |
|                            |                                                                                | erythropoietin receptor/EPOR                                                                 | 133171 | NM_00012<br>1 | 19p13.3-<br>p13.2 |
|                            |                                                                                | Janus kinase 2 (a protein tyrosine<br>kinase)/JAK2                                           | 147796 | NM_00497<br>2 | 9p24              |
|                            |                                                                                | STAM-like protein containing SH3<br>and ITAM domains 2/STAM2                                 | *****  | NM_00584<br>3 | *****             |
|                            |                                                                                | ribosomal protein S7/RPS7                                                                    | 603474 | NM_00101<br>1 | 19q13.2           |
|                            |                                                                                | signal transducer and activator of<br>transcription 5A/STAT5A                                | 601511 | NM_00315<br>2 | 17q11.2           |
|                            |                                                                                | BCL-X/BCLX                                                                                   | 600039 | Z23115        | *****             |
|                            |                                                                                | thrombopoietin (MLV oncogene<br>ligand, megakaryocyte growth and<br>development factor)/THPO | 600044 | NM_00046<br>0 | 3q26.3-q27        |
|                            |                                                                                | myeloproliferative leukemia virus<br>oncogene/MPL/thrombopoietin<br>receptor/TPOR            | 159530 | NM_00537<br>3 | 1p34              |
|                            |                                                                                | FMS-related tyrosine kinase 3/FLT3                                                           | 136351 | NM_00411<br>9 | 13q12             |

Table 4. Inflammation Gene List

| Class | Pathway | Function | Name | OMIM | GID | Locus |
|-------|---------|----------|------|------|-----|-------|
|-------|---------|----------|------|------|-----|-------|



|                                                                |                                                                                     |        |           |               |
|----------------------------------------------------------------|-------------------------------------------------------------------------------------|--------|-----------|---------------|
| <b>Major<br/>Histocompatibility<br/>Complex I</b>              | MHC class I HLA A/HLA-A                                                             | 142800 | AF148863  | 6p21.3        |
|                                                                | MHC class I HLA B/HLA-B                                                             | 142830 | NM_005514 | 6p21.3        |
|                                                                | MHC class I HLA C/HLA-C                                                             | 142840 | AF168611  | 6p21.3        |
|                                                                | MHC class I HLA E/HLA-E                                                             | 143010 | NM_005516 | 6p21.3        |
|                                                                | MHC class I HLA F/HLA-F                                                             | 143110 | X17093    | 6p21.3        |
|                                                                | MHC class I HLA G/HLA-G                                                             | 142871 | AH005893  | 6p21.3        |
| <b>Major<br/>Histocompatibility<br/>Complex I-<br/>Related</b> | beta-2-microglobulin/B2M                                                            | 109700 | NM_004048 | 15q21-q22     |
|                                                                | thymocyte antigen CD1A/CD1A                                                         | 188370 | AF142665  | 1q21-q23      |
|                                                                | thymocyte antigen CD1B/CD1B                                                         | 188360 | AF142666  | 1q21-q23      |
|                                                                | thymocyte antigen CD1C/CD1C                                                         | 188340 | AF142667  | 1q21-q23      |
|                                                                | thymocyte antigen CD1D/CD1D                                                         | 188410 | AF142668  | 1q21-q23      |
|                                                                | thymocyte antigen CD1E/CD1E                                                         | 188411 | AF142669  | 1q21-q23      |
| <b>MHC Class II<br/>Transcription</b>                          | interferon-gamma receptor 1/IFNGR1                                                  | 107470 | NM_000416 | 6q23-q24      |
|                                                                | interferon-gamma receptor 2/IFNGR2                                                  | 147569 | NM_005534 | 21q22.1-q22.2 |
|                                                                | TATA box binding protein (TBP)-associated factor, RNA polymerase II, A, 250kD/TAF2A | 313650 | NM_004606 | Xq13          |
|                                                                | interferon regulatory factor 1/IRF1                                                 | 147575 | NM_002198 | 5q31.1        |
|                                                                | nuclear factor kappa-B DNA binding subunit 2/NFKB2                                  | 164012 | NM_002502 | 10q24         |
|                                                                | MHC class II HLA DR-alpha chain/HLA-DRA                                             | 142860 | X83114    | 6p21.3        |

|                                           |                                                                     |        |           |               |
|-------------------------------------------|---------------------------------------------------------------------|--------|-----------|---------------|
| Major<br>Histocompatibility<br>Complex II | MHC class II HLA DR-beta<br>chain/HLA-DRB                           | 142857 | M11161    | 6p21.3        |
|                                           | MHC class II HLA DP-alpha<br>chain/HLA-DPA                          | 142880 | M23905    | 6p21.3        |
|                                           | MHC class II HLA DP-beta<br>chain/HLA-DPB                           | 142858 | AH002893  | 6p21.3        |
|                                           | MHC class II HLA DM-alpha<br>chain/HLA-DMA                          | 142855 | NM_006120 | 6p21.3        |
|                                           | MHC class II HLA DM-beta<br>chain/HLA-DMB                           | 142856 | NM_002118 | 6p21.3        |
|                                           | MHC class II HLA DQ-alpha<br>chain/HLA-DQA                          | 146880 | M11124    | 6p21.3        |
|                                           | MHC class II HLA DQ-beta<br>chain/HLA-DQB                           | *****  | M24364    | 6p21.3        |
|                                           | MHC class II HLA DN-alpha<br>chain/HLA-DNA                          | 142930 | X02882    | 6p21.3        |
|                                           | MHC class II HLA DO-beta<br>chain/HLA-DOB                           | 600629 | NM_002120 | 6p21.3        |
|                                           | MHC class II antigen gamma<br>chain/CD74                            | 142790 | K01144    | 5q32          |
|                                           | antigen peptide transporter 1/MHC<br>1/TAP1                         | 170260 | NM_000593 | 6p21.3        |
|                                           | antigen peptide transporter 2/MHC<br>2/TAP2                         | 170261 | NM_000544 | 6p21.3        |
|                                           | interferon-gamma receptor 1/IFNGR1                                  | 107470 | NM_000416 | 6q23-q24      |
|                                           | interferon-gamma receptor 2/IFNGR2                                  | 147569 | NM_005534 | 21q22.1-q22.2 |
|                                           | regulatory factor X, 5 (influences HLA<br>class II expression)/RFX5 | 601863 | NM_000449 | 1q21.1-q21.3  |

| Immune Discrimination<br>on<br>(Self vs Non-Self) | MHC Class II Transcription      | MHC class II transactivator/MHC2TA                                             |        | NM_000246 | 16p13         |
|---------------------------------------------------|---------------------------------|--------------------------------------------------------------------------------|--------|-----------|---------------|
|                                                   |                                 |                                                                                |        |           |               |
| Antigen Presentation and Recognition              | MHC Class II Transcription      | regulatory factor X-associated protein/RFXAP                                   | 601861 | NM_000538 | 13q14         |
|                                                   |                                 | regulatory factor X-associated ankyrin-containing protein/RFXANK               | 603200 | NM_003721 | 19p12         |
|                                                   |                                 | regulatory factor X, 2 (influences HLA class II expression)/RFX2               | 142765 | *****     | 19p13.3-p13.2 |
|                                                   |                                 | nuclear transcription factor, X-box binding 1/NFX1                             | 603255 | NM_002504 | *****         |
|                                                   |                                 | nuclear transcription factor Y, alpha/NFYA                                     | 189903 | NM_002505 | 6p21.3        |
|                                                   |                                 | nuclear transcription factor Y, beta/NFYB                                      | 189904 | NM_006166 | 12q22-q23     |
|                                                   | T-Cell Antigen Receptor Complex | T-cell antigen receptor, alpha subunit/TCRA                                    | 186880 | Z24457    | 14q11.2       |
|                                                   |                                 | T-cell antigen receptor, beta subunit/TCRB                                     | 186930 | AF011643  | 7q35          |
|                                                   |                                 | T-cell antigen receptor, gamma subunit/TCRG                                    | 186970 | M17325    | 7p15-p14      |
|                                                   |                                 | T-cell antigen receptor, delta subunit/TCRD                                    | 186810 | L36384    | 14q11.2       |
|                                                   |                                 | thymocyte antigen receptor complex CD3G, gamma polypeptide (TiT3 complex)/CD3G | 186740 | NM_000073 | 11q23         |
|                                                   |                                 | thymocyte antigen receptor complex CD3D, delta polypeptide (TiT3 complex)/CD3D | 186790 | NM_000732 | 11q23         |

|                                                  |                                                                                    |        |           |               |
|--------------------------------------------------|------------------------------------------------------------------------------------|--------|-----------|---------------|
| Rearrangement of T-Cell Antigen Receptor Complex | thymocyte antigen receptor complex CD3E, epsilon polypeptide (TiT3 complex)/CD3E   | 186830 | NM_000733 | 11q23         |
|                                                  | thymocyte antigen receptor complex CD3Z, zeta polypeptide (TiT3 complex)/CD3Z      | 186780 | NM_000734 | 1q22-q23      |
|                                                  | (p50), sheep red blood cell receptor/CD2                                           | 186990 | NM_001767 | 1p13.1        |
|                                                  | ataxia telangiectasia mutated (includes complementation groups A, C and D)/ATM     | 208900 | NM_000051 | 11q22.3       |
|                                                  | recombination activating gene 1/RAG1                                               | 179615 | NM_000448 | 11p13         |
|                                                  | recombination activating gene 2/RAG2                                               | 179616 | M94633    | 11p13         |
|                                                  | interleukin 7 receptor/IL7R                                                        | 146661 | NM_002185 | 5p13          |
|                                                  | v-myb avian myeloblastosis viral oncogene homolog/MYB                              | 189990 | NM_005375 | 6q22          |
|                                                  | core binding factor, alpha 1 subunit/CBFA1                                         | 600211 | AH005498  | 6p21          |
|                                                  | core-binding factor, beta subunit/PEBP2B/CBFB                                      | 121360 | L20298    | 16q22         |
|                                                  | ligase I, DNA, ATP-dependent/LIG1                                                  | 126391 | NM_000234 | 19q13.2-q13.3 |
|                                                  | ligase IV, DNA, ATP-dependent/LIG4                                                 | 601837 | NM_002312 | 13q22-q34     |
|                                                  | X-ray repair, complementing defect in Chinese hamster/Ku antigen, 80 kD/KU80/XRCC5 | 194364 | *****     | 2q35          |

|                                                  |                                                                                  |        |           |             |
|--------------------------------------------------|----------------------------------------------------------------------------------|--------|-----------|-------------|
|                                                  | thyroid autoantigen, 70 kD/KU70/G22P1                                            | 152690 | NM_001469 | 22q11-q13   |
| Transcription of T-Cell Antigen Receptor Complex | GATA-binding protein 3/GATA3                                                     | 131320 | NM_002051 | 10p15       |
|                                                  | long form transcription factor C-MAF/CMAF                                        | *****  | AF055377  | *****       |
|                                                  | B-cell antigen CD25/interleukin 2 receptor, alpha chain/IL2RA/CD25               | 147730 | 10p15-p14 | 10p15-p14   |
|                                                  | interleukin 2 receptor, beta/IL2RB                                               | 146710 | NM_000878 | 22q11.2-q13 |
|                                                  | interleukin 2 receptor, gamma chain/IL2RG                                        | 308380 | NM_000206 | Xq13        |
| B-Cell Antigen Receptor Complex                  | transcription factor 1/hepatic nuclear factor /HNF1/albumin proximal factor/TCF1 | 142410 | NM_000545 | 12q24.2     |
|                                                  | lymphocyte antigen CD79A/immunoglobulin-associated alpha/CD79A                   | 112205 | NM_001783 | 19q13.2     |
|                                                  | lymphocyte antigen CD79B/immunoglobulin-associated beta/CD79B                    | 147245 | L27587    | 17q23       |
|                                                  | interferon regulatory factor 1/IRF1                                              | 147575 | NM_002198 | 5q31.1      |
|                                                  | interferon regulatory factor 2/IRF2                                              | 147576 | NM_002199 | 4q35.1      |
|                                                  | interferon consensus sequence binding protein 1/ICSBP1                           | 601565 | NM_002163 | *****       |
|                                                  | interferon alpha 1/IFNA1                                                         | 147660 | X02956    | 9p22        |
|                                                  | interferon alpha 2/IFNA2                                                         | 147562 | Y11834    | 9p22        |

|                    |                  |                                                      |        |                       |          |
|--------------------|------------------|------------------------------------------------------|--------|-----------------------|----------|
| <b>Interferons</b> | <b>Synthesis</b> | interferon alpha 4/IFNA4                             | 147564 | *****                 | 9p22     |
|                    |                  | interferon alpha 5/IFNA5                             | 147565 | NM_00216 <sub>9</sub> | 9p22     |
|                    |                  | interferon alpha 6/IFNA6                             | 147566 | *****                 | 9p22     |
|                    |                  | interferon alpha 7/IFNA7                             | 147567 | *****                 | 9p22     |
|                    |                  | interferon alpha 8/IFNA8                             | 147568 | NM_00217 <sub>0</sub> | 9p22     |
|                    |                  | interferon alpha 10/IFNA10                           | 147577 | NM_00217 <sub>1</sub> | 9p22     |
|                    |                  | interferon alpha 13/IFNA13                           | 147578 | NM_00690 <sub>0</sub> | 9p22     |
|                    |                  | interferon alpha 14/IFNA14                           | 147579 | NM_00217 <sub>2</sub> | 9p22     |
|                    |                  | interferon alpha 16/IFNA16                           | 147580 | NM_00217 <sub>3</sub> | 9p22     |
|                    |                  | interferon alpha 17/IFNA17                           | 147583 | *****                 | 9p22     |
|                    |                  | interferon alpha 21/IFNA21                           | 147584 | NM_00217 <sub>5</sub> | 9p22     |
|                    |                  | interferon beta 1/IFNB1                              | 147640 | NM_00217 <sub>6</sub> | 9p21     |
|                    |                  | interferon beta 3/IFNB3                              | 147860 | K03196                | Chr.8    |
|                    |                  | interferon gamma/IFNG                                | 147570 | L07633                | 12q14    |
|                    |                  | interferon omega 1/IFNW1                             | 147553 | NM_00217 <sub>7</sub> | 9p21     |
|                    | <b>Receptors</b> | interferon (alpha, beta and omega) receptor 1/IFNAR1 | 107450 | X77722                | 21q22.1  |
|                    |                  | interferon (alpha, beta and omega) receptor 2/IFNAR2 | 602376 | NM_00087 <sub>4</sub> | 21q22.1  |
|                    |                  | interferon-gamma receptor 1/IFNGR1                   | 107470 | NM_00041 <sub>6</sub> | 6q23-q24 |

|                                                                                               |        |           |               |
|-----------------------------------------------------------------------------------------------|--------|-----------|---------------|
| interferon-gamma receptor 2/IFNGR2                                                            | 147569 | NM_005534 | 21q22.1-q22.2 |
| interleukin enhancer binding factor 1/ILF1                                                    | 147685 | NM_004514 | 17q25         |
| interleukin enhancer binding factor 2, 45 kD/ILF2                                             | 603181 | NM_004515 | *****         |
| interleukin enhancer binding factor 3, 90 kD/ILF3                                             | 603182 | NM_004516 | *****         |
| interleukin 1 alpha/IL1A2                                                                     | 147761 | M15330    | 3q14          |
| interleukin 1 beta/IL1B                                                                       | 147720 | AF043335  | 2q14          |
| apoptosis-related cystein protease 1/interleukin 1-beta converting enzyme/ICE/caspase 1/CASP1 | 147678 | NM_001223 | 11q22.2-q22.3 |
| interleukin 2/IL2                                                                             | 147680 | X01586    | 4q26-q27      |
| interleukin 3/IL3                                                                             | 147740 | NM_000588 | 5q31.1        |
| interleukin 4/IL4                                                                             | 147780 | NM_000589 | 5q31.1        |
| interleukin 5/IL5                                                                             | 147850 | NM_000879 | 5q31.1        |
| interleukin 6/IL6                                                                             | 147620 | AF048692  | 7p21          |
| interleukin 7/IL7                                                                             | 146660 | NM_000880 | 8q12-q13      |
| interleukin 8/IL8                                                                             | 146930 | M26383    | 4q12-q13      |
| interleukin 9/IL9                                                                             | 146931 | X17543    | 5q31.1        |
| interleukin 10/IL10                                                                           | 124092 | M57627    | 1q31-q32      |
| interleukin 11 beta/IL11B                                                                     | 147681 | NM_000881 | 19q13.3-q13.4 |

Synthesis

|              |                                                                                                                 |        |           |               |
|--------------|-----------------------------------------------------------------------------------------------------------------|--------|-----------|---------------|
| Interleukins | interleukin 12A (natural killer cell stimulatory factor 1, cytotoxic lymphocyte maturation factor 1, p35)/IL12A | 161560 | NM_002187 | 3p12-q13.2    |
|              | interleukin 12B/IL12B                                                                                           | 161561 | NM_000440 | 5q31.1-q33.1  |
|              | interleukin 13/IL13                                                                                             | 147683 | NM_002188 | 5q31          |
|              | interleukin 15/IL15                                                                                             | 600554 | U14407    | 4q31          |
|              | interleukin 16/IL16                                                                                             | 603035 | NM_004513 | *****         |
|              | interleukin 17 (cytotoxic T-lymphocyte-associated serine esterase 3)/IL17                                       | 603149 | NM_002190 | 2q31          |
|              | interleukin 18 (interferon-gamma-inducing factor)/IL18                                                          | 600953 | NM_001562 | 11q22.2-q22.3 |
|              | interleukin 1 receptor, type 1/IL1R1                                                                            | 147810 | NM_000877 | 2q12          |
|              | interleukin 1 receptor, type 2/IL1R2                                                                            | 147811 | NM_004633 | 2q12-q22      |
|              | interleukin 1 receptor-like 2/IL1RL2                                                                            | *****  | NM_003854 | *****         |
|              | interleukin 1 receptor accessory protein/IL1RAP                                                                 | 602626 | NM_002182 | 3q28          |
|              | B-cell antigen CD25/interleukin 2 receptor, alpha chain/IL2RA/CD25                                              | 147730 | 10p15-p14 | 10p15-p14     |
|              | interleukin 2 receptor, beta/IL2RB                                                                              | 146710 | NM_000878 | 22q11.2-q13   |
|              | interleukin 2 receptor, gamma chain/IL2RG                                                                       | 308380 | NM_000206 | Xq13          |
|              | interleukin 3 alpha receptor/IL3RA                                                                              | 308385 | M74782    | Xp22.3        |



|           |                                                   |        |           |               |
|-----------|---------------------------------------------------|--------|-----------|---------------|
| Receptors | interleukin 4 receptor precursor/IL4R             | 147781 | NM_000418 | 16p12.1-p11.2 |
|           | interleukin 5 receptor alpha/IL5RA                | 147851 | M96652    | 3p26-p24:     |
|           | interleukin 6 receptor/IL6R                       | 147880 | NM_000565 | 1q21          |
|           | interleukin 7 receptor/IL7R                       | 146661 | NM_002185 | 5p13          |
|           | interleukin 9 receptor/IL9R                       | 300007 | NM_002186 | Xq28          |
|           | interleukin 10 receptor, alpha/IL10RA             | 146933 | NM_001558 | 11q23.3       |
|           | interleukin 10 receptor beta/IL10RB               | *****  | NM_000628 | *****         |
|           | interleukin receptor 11 alpha/IL11RA              | 600939 | NM_004512 | 9p13          |
|           | interleukin 12 receptor, beta 1/IL12RB1           | 600939 | NM_005535 | 9p13          |
|           | interleukin 12 receptor, beta 2/IL12RB2           | 601642 | NM_001559 | 1p31.2        |
|           | interleukin 13 receptor, alpha 1/IL13RA1          | 300119 | NM_001560 | Chr.X         |
|           | interleukin receptor 13 alpha2/IL13A2             | 300130 | X95302    | Xq24          |
|           | interleukin 15 receptor, alpha/IL15RA             | 601070 | NM_002189 | 10p15-p14     |
|           | interleukin 18 receptor 1/IL18R1                  | *****  | NM_003855 | *****         |
|           | interleukin 18 receptor accessory protein/IL18RAP | *****  | NM_003853 | *****         |
|           | LPS-Induced TNF-Alpha Factor/LITAF                | 603795 | U77396    | 16p13.3-p12   |

|           |                                    |        |          |              |
|-----------|------------------------------------|--------|----------|--------------|
| Synthesis | tumor necrosis factor alpha/TNFA   | 191160 | X01394   | 6p21.3       |
|           | tumor necrosis factor              |        | NM_00059 |              |
|           | beta/TNFB/lymphotoxin alpha/LTA    | 153440 | 5        | 6p21.3       |
|           | tumor necrosis factor              |        | NM_00234 |              |
|           | C/TNFC/lymphotoxin-beta/LTB        | 600978 | 1        | 6p21.3       |
|           | tumor necrosis factor ligand       |        | NM_00332 |              |
|           | superfamily, member 4/TNFSF4       | 603594 | 6        | 1q25         |
|           | tumor necrosis factor ligand       |        | NM_00007 |              |
|           | superfamily, member 5/TNFSF5       | 308230 | 4        | Xq26         |
|           | tumor necrosis factor ligand       |        | NM_00063 |              |
|           | superfamily, member 6/TNFSF6       | 134638 | 9        | 1q23         |
|           | B-cell antigen CD70/tumor necrosis |        |          |              |
|           | factor ligand superfamily, member  |        | NM_00125 |              |
|           | 7/TNFSF7/CD27 ligand/CD70          | 602840 | 2        | 19p13        |
|           | tumor necrosis factor ligand       |        | NM_00124 |              |
|           | superfamily, member 8/TNFSF8       | 603875 | 4        | 9q33         |
|           | tumor necrosis factor ligand       |        | NM_00381 |              |
|           | superfamily, member 10/TNFSF10     | 603598 | 0        | 3q26         |
|           | tumor necrosis factor ligand       |        | NM_00370 |              |
|           | superfamily, member 11/TNFSF11     | 602642 | 1        | 13q14        |
|           | tumor necrosis factor ligand       |        | NM_00380 |              |
|           | superfamily, member 12/TNFSF12     | 602695 | 9        | 17p13.3      |
|           | tumor necrosis factor ligand       |        | NM_00657 |              |
|           | superfamily, member 13B/TNFSF13B   | 603969 | 3        | 13q32-q34    |
|           | tumor necrosis factor ligand       |        | *****    |              |
|           | superfamily, member 15/TNFSF15     | 604052 |          | 9q33         |
|           | tumor necrosis factor receptor     |        | NM_00106 |              |
|           | superfamily, member 1A/TNFRSF1A    | 191190 | 5        | 12p13.2      |
|           | tumor necrosis factor receptor     |        | NM_00106 |              |
|           | superfamily, member 1B/TNFRSF1B    | 191191 | 6        | 1p36.3-p36.2 |

|                                                                                                 |        |               |                 |
|-------------------------------------------------------------------------------------------------|--------|---------------|-----------------|
| lymphotoxin beta receptor (TNFR<br>superfamily, member 3/LTBR                                   | 600979 | NM_00234<br>2 | 12p13           |
| tumor necrosis factor receptor<br>superfamily, member 4/TNFRSF4                                 | 600315 | NM_00332<br>7 | 1p36            |
| B-cell antigen CD40/tumor necrosis<br>factor receptor superfamily, member<br>5/CD40/TNFRSF5     | 109535 | NM_00125<br>0 | 20q12-<br>q13.2 |
| lymphocyte antigen CD95/tumor<br>necrosis factor receptor superfamily,<br>member 6/TNFRSF6/CD95 | 134637 | NM_00004<br>3 | 10q24.1         |
| tumor necrosis factor receptor<br>superfamily, member 6B/TNFRSF6B                               | 603361 | NM_00382<br>3 | 20q13           |
| T-cell antigen CD27/tumor necrosis<br>factor receptor superfamily, member<br>7/CD27/TNFRSF7     | 186711 | M63928        | 12p13           |
| lymphocyte antigen CD30/tumor<br>necrosis factor receptor superfamily,<br>member 8/CD30/TNFRSF8 | 153243 | NM_00124<br>3 | 1p36            |
| tumor necrosis factor receptor<br>superfamily, member 9/TNFRSF9                                 | 602250 | NM_00156<br>1 | 1p36            |
| tumor necrosis factor receptor<br>superfamily, member                                           | 603611 | NM_00384<br>4 | 8p21            |
| tumor necrosis factor receptor<br>superfamily, member                                           | 603612 | NM_00384<br>2 | 8p22-p21        |
| tumor necrosis factor receptor<br>superfamily, member                                           | 603613 | AF014794      | 8p22-p21        |
| tumor necrosis factor receptor<br>superfamily, member                                           | 603614 | NM_00384<br>0 | 8p21            |
| tumor necrosis factor receptor<br>superfamily, member                                           | 603499 | NM_00383<br>9 | 18q22.1         |

### Receptors

**Tumor  
Necrosis  
Factor  
Ligand  
Superfamily**

|                            |           |                                                                                                   |        |           |              |
|----------------------------|-----------|---------------------------------------------------------------------------------------------------|--------|-----------|--------------|
| Transforming Growth Factor | Synthesis | tumor necrosis factor receptor superfamily, member 11/TNFRSF11B                                   | 602643 | NM_002546 | 8q24         |
|                            |           | tumor necrosis factor receptor superfamily, member 12/TNFRSF12                                    | 603366 | NM_003790 | 1p36.3       |
|                            |           | tumor necrosis factor receptor superfamily, member 14/TNFRSF14                                    | 602746 | NM_003820 | 1p36.3-p36.2 |
|                            |           | tumor necrosis factor receptor superfamily, member 16/TNFRSF16                                    | 162010 | NM_002507 | 17q21-q22    |
|                            |           | tumor necrosis factor receptor superfamily, member 17/TNFRSF17                                    | 109545 | Z14954    | 16p13.1      |
|                            |           | tumor necrosis factor receptor superfamily, member 18/TNFRSF18                                    | 603905 | *****     | 1p36.3       |
|                            |           | transforming growth factor, transforming growth factor, beta-1/TGFB1                              | 190170 | NM_003236 | 2p13         |
|                            |           | transforming growth factor, beta-2/TGFB2                                                          | 190180 | M60315    | 9q13.1-q13.2 |
|                            |           | transforming growth factor, beta-3/TGFB3                                                          | 190220 | NM_003238 | 1q41         |
|                            | Receptors | growth differentiation factor 1/GDF1                                                              | 190230 | NM_003239 | 14q24        |
|                            |           | transforming growth factor, beta receptor I (activin A receptor type II-like kinase, 53kD)/TGFBRI | 602880 | NM_001492 | 19p12        |
|                            |           | transforming growth factor, beta receptor II (70-80kD)/TGFBRII                                    | 190181 | NM_004612 | 9q33-q34     |
|                            |           | transforming growth factor, beta receptor III (betaglycan, 300kD)/TGFBRIII                        | 190182 | NM_003242 | 3p22         |
|                            |           | transforming growth factor, beta receptor III (betaglycan, 300kD)/TGFBRIII                        | 600742 | NM_003243 | 1p33-p32     |

|                                                                                                                        |        |               |                 |
|------------------------------------------------------------------------------------------------------------------------|--------|---------------|-----------------|
| small inducible cytokine subfamily A<br>(Cys-Cys), member 1/ inflammatory<br>cytokine I309/SCYA1                       | 182281 | NM_00298<br>1 | Chr.17          |
| small inducible cytokine subfamily A<br>(Cys-Cys), member 2/monocyte<br>chemotactic protein 1/MCP1/SCYA2               | 158105 | NM_00298<br>2 | 17q11.2-<br>q12 |
| small inducible cytokine subfamily A<br>(Cys-Cys), member 3/macrophage<br>inflammatory protein<br>1A/MIP1A/SCYA3       | 182283 | NM_00298<br>3 | 17q11-q21       |
| small inducible cytokine subfamily A<br>(Cys-Cys), member 3-like 1/LD78-<br>beta/SCYA3LI                               | 601395 | D90144        | 17q11.2         |
| small inducible cytokine subfamily A<br>(Cys-Cys), member 4/macrophage<br>inflammatory protein<br>1B/MIP1B/SCYA4       | 182284 | NM_00298<br>4 | 17q21-q23       |
| small inducible cytokine subfamily A<br>(Cys-Cys), member 4-like/macrophage<br>inflammatory protein<br>1B/MIP1B/SCYA4L | 603782 | X52149        | 17q11.2         |
| small inducible cytokine subfamily A<br>(Cys-Cys), member 5/T-cell specific<br>protein p228/TCP228/SCYA5               | 187011 | NM_00298<br>5 | 17q11.2-<br>q12 |
| small inducible cytokine subfamily A<br>(Cys-Cys), member 6/SCYA6                                                      | *****  | *****         | *****           |
| small inducible cytokine subfamily A<br>(Cys-Cys), member 7/monocyte<br>chemotactic protein 3/MCP3/SCYA7               | 158106 | AF043338      | 17q11.2-<br>q12 |

|                                                                                                                          |        |               |                   |
|--------------------------------------------------------------------------------------------------------------------------|--------|---------------|-------------------|
| small inducible cytokine subfamily A<br>(Cys-Cys), member 8/monocyte<br>chemotactic protein 2/MCP2/SCYA8                 | 602283 | NM_00562<br>3 | 17q11.2           |
| small inducible cytokine subfamily A<br>(Cys-Cys), member<br>9/10/SCYA9SCY10                                             | *****  | *****         | *****             |
| small inducible cytokine subfamily A<br>(Cys-Cys), member<br>11/eotaxin/SCYA11                                           | 601156 | NM_00298<br>6 | 17q21.1-<br>q21.2 |
| small inducible cytokine subfamily A<br>(Cys-Cys), member 12/SCYA12                                                      | *****  | *****         | *****             |
| small inducible cytokine subfamily A<br>(Cys-Cys), member 13/monocyte<br>chemotactic protein 4/MCP4/SCYA13               | 601391 | NM_00540<br>8 | 17q11.2           |
| small inducible cytokine subfamily A<br>(Cys-Cys), member 14/new cc<br>chemokine 2/NCC2/SCYA14                           | 601392 | NM_00459<br>0 | 17q11.2           |
| small inducible cytokine subfamily A<br>(Cys-Cys), member 15/leukotactin<br>1/LKN1/SCYA15                                | 601393 | NM_00416<br>7 | 17q11.2           |
| small inducible cytokine subfamily A<br>(Cys-Cys), member 16/new cc<br>chemokine 4/NCC4/SCYA16                           | 601394 | NM_00459<br>0 | 17q11.2           |
| small inducible cytokine subfamily A<br>(Cys-Cys), member 17/thymus and<br>activation-regulated<br>chemokine/TARC/SCYA17 | 601520 | NM_00298<br>7 | 16q13             |

|                                                                                                                             |        |               |          |
|-----------------------------------------------------------------------------------------------------------------------------|--------|---------------|----------|
| small inducible cytokine subfamily A<br>(Cys-Cys), member 18/pulmonary and<br>activation-regulated<br>chemokine/PARC/SCYA18 | 603757 | NM_00298<br>8 | 17q11.2  |
| small inducible cytokine subfamily A<br>(Cys-Cys), member 19/macrophage<br>inflammatory protein<br>3B/MIP3B/SCYA19          | 602227 | NM_00627<br>4 | 9p13     |
| small inducible cytokine subfamily A<br>(Cys-Cys), member 20/macrophage<br>inflammatory protein<br>3A/MIP3A/exodus 1/SCYA20 | 601960 | NM_00459<br>1 | 2q33-q37 |
| small inducible cytokine subfamily A<br>(Cys-Cys), member 21/secondary<br>lymphoid tissue<br>chemokine/SLC/exodus 2/SCYA21  | 602737 | NM_00298<br>9 | 9p13     |
| small inducible cytokine subfamily A<br>(Cys-Cys), member 22/SCYA22                                                         | 602957 | NM_00299<br>0 | 16q13    |
| small inducible cytokine subfamily A<br>(Cys-Cys), member 23/myeloid<br>progenitor inhibitory factor<br>1/MPIF1/SCYA23      | 602494 | NM_00506<br>4 | *****    |
| small inducible cytokine subfamily A<br>(Cys-Cys), member 24/myeloid<br>progenitor inhibitory factor<br>2/MPIF2/SCYA24      | 602495 | NM_00299<br>1 | 7q11.23  |
| small inducible cytokine subfamily A<br>(Cys-Cys), member 25/thymus-<br>expressed chemokine/TECK/SCYA25                     | 602565 | NM_00562<br>4 | 19p13.2  |

**Synthesis**  
(see also  
signaling and  
transcription  
factors  
below)

**Cytokine-  
Mediated  
Immune  
Regulation**

|                                                                                                                                |        |           |          |
|--------------------------------------------------------------------------------------------------------------------------------|--------|-----------|----------|
| Chemokines                                                                                                                     | *****  | AA716120  | Chr. 7   |
| small inducible cytokine subfamily A<br>(Cys-Cys), member 26/eotaxin<br>3/SCYA26                                               | *****  | *****     | Chr. 9   |
| small inducible cytokine subfamily A<br>(Cys-Cys), member 27/ALP/SCYA27                                                        | 155730 | NM_001511 | 4q12-q13 |
| small inducible cytokine subfamily B<br>(Cys-X-Cys), member 1/SCXB1                                                            | 139110 | NM_002089 | 4q12-q13 |
| small inducible cytokine subfamily B<br>(Cys-X-Cys), member 2/SCXB2                                                            | 139111 | AA935273  | 4q12-q13 |
| small inducible cytokine subfamily B<br>(Cys-X-Cys), member 3/SCXB3                                                            | 173460 | NM_002619 | 4q12-q13 |
| small inducible cytokine subfamily B<br>(Cys-X-Cys), member 4/SCXB4/platelet factor 4/PF4                                      | 600324 | NM_002994 | 4q13-q21 |
| small inducible cytokine subfamily B<br>(Cys-X-Cys), member 5/epithelial-<br>derived neutrophil-activating peptide<br>78/SCXB5 | 138965 | U83303    | 4q12-q21 |
| small inducible cytokine subfamily B<br>(Cys-X-Cys), member 6/granulocyte<br>chemotactic protein 2/GCP2/SCXB6                  | 121010 | NM_002704 | 4p12-q13 |
| small inducible cytokine subfamily B<br>(Cys-X-Cys), member 7/SCXB7                                                            | 146930 | M26383    | 4q12-q13 |
| small inducible cytokine subfamily B<br>(Cys-X-Cys), member 8/SCXB8/<br>interleukin 8/IL8                                      | 601704 | AA037522  | 4q21     |
| small inducible cytokine subfamily B<br>(Cys-X-Cys), member 9/SCXB9                                                            |        |           |          |



|                                                                                                                                |        |               |          |
|--------------------------------------------------------------------------------------------------------------------------------|--------|---------------|----------|
| small inducible cytokine subfamily B<br>(Cys-X-Cys), member<br>10/SCYB10interferon (gamma)-<br>induced protein of 10 kDa/INP10 | 147310 | NM_00156<br>5 | 4q21     |
| small inducible cytokine subfamily B<br>(Cys-X-Cys), member 11/SCYB11                                                          | *****  | AA361853      | Chr. 4   |
| small inducible cytokine subfamily B<br>(Cys-X-Cys), member<br>12/SCYB12/stromal cell-driven<br>factor/SDF1                    | 600835 | L36033        | 10q11.1  |
| small inducible cytokine subfamily B<br>(Cys-X-Cys), member 13/SCYB13                                                          | *****  | *****         | *****    |
| small inducible cytokine subfamily B<br>(Cys-X-Cys), member 14/SCYB14                                                          | 604186 | AC005738      | 5q31     |
| small inducible cytokine subfamily C,<br>member 1/lymphotactin/LTN/SCYC1                                                       | 600250 | NM_00299<br>5 | 1q21-q25 |
| small inducible cytokine subfamily C,<br>member 2/SCYC2                                                                        | *****  | NM_00317<br>5 | *****    |
| small inducible cytokine subfamily D<br>(Cys-X3-Cys), member<br>1/fractalkine/neurotactin/NTT/NTN/S<br>CYD1                    | 601880 | NM_00299<br>6 | 16q      |
| chemokine (C-C motif) receptor<br>1/MIP1A receptor/CCR1                                                                        | 601159 | NM_00129<br>5 | 3p21     |
| chemokine (C-C motif) receptor<br>2/MCP1 receptor/CCR2                                                                         | 601267 | NM_00064<br>7 | 3p21     |
| chemokine (C-C motif) receptor<br>3/eotaxin receptor/CCR3                                                                      | 601268 | NM_00183<br>7 | 3p21.3   |
| chemokine (C-C motif) receptor<br>4/CCR4                                                                                       | *****  | NM_00550<br>8 | *****    |

|                                                                                    |        |           |                  |
|------------------------------------------------------------------------------------|--------|-----------|------------------|
| chemokine (C-C motif) receptor<br>5/CCR5                                           | 601373 | NM_000579 | 3p21             |
| chemokine (C-C motif) receptor 6/G<br>protein-coupled receptor<br>29/GPR29/CCR6    | 601835 | NM_004367 | 6q27             |
| chemokine (C-C motif) receptor<br>7/epstein-barr virus induced gene<br>1/EBI1/CCR7 | 600242 | NM_001838 | 17q12-<br>q21.2  |
| chemokine (C-C motif) receptor<br>8/CCR8                                           | 601834 | NM_005201 | 3p22             |
| chemokine (C-C motif) receptor<br>9/chemokine-binding protein<br>2/CCBP2/CCR9      | 602648 | NM_006641 | 3p21.3           |
| chemokine (C-C motif) receptor<br>10/CCR10                                         | *****  | U94888    | *****            |
| chemokine (C-X-C motif), receptor<br>3/G protein-coupled receptor<br>9/GPR9/CXCR3  | 600894 | NM_001504 | 8p12-p11.2       |
| chemokine (C-X-C motif), receptor<br>4/fusin/CXCR4                                 | 162643 | NM_003467 | 2q21             |
| chemokine (C-X3-C motif), receptor<br>1/fractalkine receptor/CX3CR1                | 601470 | NM_001337 | 3pter-p21        |
| interleukin 8 receptor, alpha/IL8RA                                                | 146929 | NM_000634 | 2q35             |
| interleukin 8 receptor beta/IL8RB                                                  | 146928 | NM_001557 | 2q35             |
| chemokine (C motif) XC receptor 1/G<br>protein-coupled receptor<br>5/GPR5/CCXCR1   | 600552 | NM_005283 | 3p21.3-<br>p21.1 |

**C-Motif  
Chemokine  
Receptors**

|                      |           |                                                                                  |        |           |               |
|----------------------|-----------|----------------------------------------------------------------------------------|--------|-----------|---------------|
| Other Growth Factors | Synthesis | macrophage migration-inhibitory factor (glycosylation-inhibiting factor) GM-6000 | 153620 | NM_002415 | 22q11.2       |
|                      |           | leukemia inhibitory factor/LIF                                                   | 159540 | NM_002309 | 22q12.1-q12.2 |
|                      |           | oncostatin M                                                                     | 165095 | AF129855  | 22q12.1-q12.2 |
|                      |           | ciliary neurotrophic factor/CNTF                                                 | 118945 | NM_000614 | 11q12.2       |
|                      |           | epidermal growth factor/EGF                                                      | 131530 | NM_001963 | 4q25          |
|                      |           | pre-B cell stimulating factor homologue/SDF1A                                    | 600835 | L36034    | 10q11.1       |
|                      |           | cardiotrophin 1                                                                  | 600435 | *****     | *****         |
|                      |           | mast cell growth factor/MGF                                                      | 184745 | NM_003994 | 12q22         |
|                      |           | granulocyte-macrophage colony stimulating factor 2/CSF2                          | 138960 | NM_000758 | 5q31.1        |
|                      |           | macrophage-specific colony-stimulating factor/CSF1                               | 120420 | AH005300  | 1p21-p13      |
|                      |           | granulocyte colony stimulating factor 3/CSF3                                     | 138970 | NM_000759 | 17q11.2-q12   |
|                      |           | epidermal growth factor receptor EGFR                                            | 131550 | NM_005228 | 7p12.3-p12.1  |
|                      |           | ciliary neurotrophic factor receptor/CNTFR                                       | 118946 | NM_001842 | 9p13          |
|                      |           | oncostatin M receptor/OSMR                                                       | 601743 | NM_003999 | *****         |
|                      |           | neutrophil chemotactic response receptor/gpl30                                   | 162820 | *****     | 7q22-qter     |

|                  |                                                                                          |        |           |                |
|------------------|------------------------------------------------------------------------------------------|--------|-----------|----------------|
| <b>Receptors</b> | colony stimulating factor 1 receptor/CSFR1                                               | 164770 | U63963    | 5q33.2-q33.3   |
|                  | granulocyte-macrophage colony stimulating factor 2 receptor, alpha, low-affinity/CSF2RA  | 306250 | NM_006140 | Xp22.32        |
|                  | granulocyte-macrophage colony stimulating factor 2 receptor, beta/CSF2RB                 | 138981 | U18373    | 22q12.2-q13.1  |
|                  | granulocyte-macrophage colony stimulating factor 2 receptor, alpha, Y chromosomal/CSF2RY | 425000 | *****     | Yp11           |
|                  | myelocyte antigen CD105/endoglin/ENG/TGFB receptor component/CD105                       | 131195 | NM_000118 | 9q34.1         |
|                  | leukocyte antigen CD 97/CD97                                                             | 601211 | NM_001784 | 19p13.2-p13.12 |
|                  | signal transducer and activator of transcription 1/STAT 1                                | 600555 | *****     | 2q32.2-q32.3   |
|                  | signal transducer and activator of transcription 2, 113kD/STAT2                          | 600556 | NM_005419 | *****          |
|                  | signal transducer and activator of transcription 3/STAT3                                 | 102582 | NM_003150 | 17q21          |
|                  | signal transducer and activator of transcription 6, interleukin-4 induced/STAT6          | 601512 | NM_003153 | 12q13          |
|                  | signal transducing adaptor molecule (SH3 domain and ITAM motif) 1/STAM                   | 601899 | NM_003473 | 10p14-p13      |
|                  | STAM-like protein containing SH3 and ITAM domains 2/STAM2                                | *****  | NM_005843 | *****          |

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|----------------------------------------------------------------------------------------|--------|-----------|---------------|
| interferon-stimulated transcription factor 3, gamma (48kD)/ISGF3G                      | 147574 | NM_006084 | 14q11.2       |
| interferon, alpha-inducible protein 27/IFI27                                           | 600009 | NM_005532 | 14q32         |
| interferon, alpha-inducible protein (clone IFI-6-16)/GIP3                              | 147572 | NM_002038 | 1p35          |
| Janus kinase 1 (protein tyrosine kinase)/JAK1                                          | 147795 | NM_002227 | 1p31.3        |
| Janus kinase 3 (protein tyrosine kinase)/JAK3                                          | 600173 | NM_000215 | 19p13.1       |
| interleukin-1 receptor-associated kinase M/IRAK-M                                      | *****  | NM_007199 | *****         |
| interleukin-1 receptor-associated kinase 1/IRAK1                                       | 601108 | NM_001569 | Xq28          |
| interleukin-1 receptor-associated kinase 1/IRAK2                                       | 603304 | NM_001570 | *****         |
| nuclear factor, interleukin 3 regulated/NFIL3                                          | *****  | NM_005384 | *****         |
| nuclear factor of activated T-cells, cytoplasmic 1/NFATC1                              | 600489 | NM_006162 | 18q23         |
| nuclear factor of activated T-cells, cytoplasmic 2/NFATC2                              | 600490 | *****     | 20q13.2-q13.3 |
| nuclear factor of activated T-cells, cytoplasmic 3/NFATC3                              | 602698 | L41066    | 16q13-q24     |
| nuclear factor of activated T-cells, cytoplasmic 4/NFATC4                              | 602699 | L41067    | *****         |
| caspase 1, apoptosis-related cysteine protease (interleukin 1, beta, convertase)/CASPI | 147678 | NM_001223 | 11q22.2-q22.3 |

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| TGFB inducible early growth response/TIEG                                                  | 601878 | NM_005655 | *****         |
| TGFB inducible early growth response 2/TIEG2                                               | 603301 | NM_003597 | *****         |
| eukaryotic translation initiation factor 3, subunit 8 (110kD)/EIF3S8                       | 603911 | NM_003752 | 1p34.1        |
| MAD (mothers against decapentaplegic) homolog 1/MADH1                                      | 601595 | NM_005900 | 4q28          |
| homolog of Xenopus forkhead activin signal transducer-1 /FAST1                             | 603621 | NM_003923 | 8q24.3        |
| interleukin 1 receptor accessory protein/IL1RAP                                            | 602626 | NM_002182 | 3q28          |
| CCAAT/enhancer binding protein (C/EBP), delta/CEBPD                                        | 189965 | NM_005195 | 20q13.1       |
| T-lymphocytes-specific interleukin 2 inhibitor/transcription factor 8/TCF8/                | 189909 | U12170    | 10p11.2       |
| cAMP responsive element binding protein 1/CREB1                                            | 123810 | NM_004379 | 2q32.3-q34    |
| interferon-stimulated transcription factor 3, gamma (48kD)/ISGF3G                          | 147574 | NM_006084 | 14q11.2       |
| interferon regulatory factor 3/IRF3                                                        | 603734 | NM_001571 | 19q13.3-q13.4 |
| lymphocyte specific interferon regulatory factor/LSIRF/interferon regulatory factor 4/IRF4 | 601900 | U52683    | 6p25-p23      |
| TNF receptor-associated factor 1/TRAF1                                                     | 601711 | NM_005658 | 9q33-q34      |
| TNF receptor-associated factor 2/TRAF2                                                     | 601895 | U12597    | 9q34          |

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|----------------------|----------------------------------------------|--------------------------------------------------------|--------|---------------|-----------|
| Cytokine<br>Response | Signaling<br>and<br>Transcription<br>Factors | TNF receptor-associated factor<br>3/TRAF3              | 601896 | NM_00330<br>0 | *****     |
|                      |                                              | TNF receptor-associated factor<br>4/TRAF4              | 602464 | NM_00429<br>5 | 17q11-q12 |
|                      |                                              | TNF receptor-associated factor<br>5/TRAF5              | 602356 | AB000509      | 1q32      |
|                      |                                              | TNF receptor-associated factor<br>6/TRAF6              | 602355 | NM_00462<br>0 | *****     |
|                      |                                              | TRAF family member-associated<br>NFKB activator/TANK   | 603893 | NM_00418<br>0 | 2q24-q31  |
|                      |                                              | mitogen activated protein kinase<br>PRKM1/MAPK1        | 176948 | NM_00274<br>5 | 22q11.2   |
|                      |                                              | mitogen activated protein kinase<br>PRKM3/MAPK3        | 601795 | X60188        | 16p11.2   |
|                      |                                              | mitogen activated protein kinase<br>PRKM4/MAPK4        | 176949 | NM_00274<br>7 | 18q12-q21 |
|                      |                                              | mitogen activated protein kinase<br>PRKM6/MAPK6        | 602904 | NM_00274<br>8 | *****     |
|                      |                                              | mitogen activated protein kinase<br>PRKM7/MAPK7        | 602521 | NM_00274<br>9 | 17p11.2   |
|                      |                                              | mitogen activated protein kinase<br>JNK1/PRKM8/MAPK8   | 601158 | L26318        | *****     |
|                      |                                              | mitogen activated protein kinase<br>JNK2/PRKM9/MAPK9   | 602896 | U09759        | 5q35      |
|                      |                                              | mitogen activated protein kinase<br>JNK3/PRKM10/MAPK10 | 602897 | U35003        | *****     |
|                      |                                              | mitogen activated protein kinase<br>PRKM11/MAPK11      | 602898 | AF031135      | *****     |
|                      |                                              | mitogen activated protein kinase<br>SAPK3/MAPK12       | 602399 | NM_00296<br>9 | 22q13.3   |

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| mitogen activated protein kinase<br>PRKM13/MAPK13   | 602899 | NM_00275<br>4 | *****              |
| mitogen activated protein kinase<br>SAPK2A/MAPK14   | 600289 | NM_00131<br>5 | 6p21.3-<br>p21.2   |
| mitogen-activated protein kinase<br>kinase 1/MAP2K1 | 176872 | NM_00275<br>5 | 15q22.1-<br>q22.33 |
| mitogen-activated protein kinase<br>kinase 2/MAP2K2 | 601263 | L11285        | *****              |
| mitogen-activated protein kinase<br>kinase 3/MAP2K3 | 602315 | NM_00275<br>6 | 17q11.2            |
| mitogen-activated protein kinase<br>kinase 4/MAP2K4 | 601335 | NM_00301<br>0 | 17p11.2            |
| mitogen-activated protein kinase<br>kinase 5/MAP2K5 | 602520 | NM_00275<br>7 | *****              |
| mitogen-activated protein kinase<br>kinase 6/MAP2K6 | 601254 | U39065        | *****              |
| mitogen-activated protein kinase<br>kinase 7/MAP2K7 | 603014 | NM_00504<br>3 | *****              |
| protein kinase C alpha/PRKCA                        | 176960 | NM_00273<br>7 | 17q22-<br>q23.2    |
| protein kinase C beta/PRKCB                         | 176970 | X06318        | 16p11.2            |
| protein kinase C, delta/PRKCD                       | 176977 | NM_00625<br>4 | 3p                 |
| protein kinase C gamma/PRKCG                        | 176980 | *****         | 19q13.4            |
| protein kinase C, theta/PRKCT                       | 600448 | NM_00625<br>7 | 10p15              |
| protein kinase C, zeta/PRKCZ                        | 176982 | NM_00274<br>4 | *****              |
| casein kinase 1 alpha 1                             | 600505 | NM_00189<br>2 | 13q13              |



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| casein kinase 1 gamma 2                                                                    | 602214 | U89896        | 19p13.3           |
| casein kinase 1 delta                                                                      | 600864 | NM_00189<br>3 | 17q25             |
| casein kinase 1 epsilon                                                                    | 600863 | NM_00189<br>4 | 22q12-q13         |
| casein kinase 2 alpha 1                                                                    | 115440 | J02853        | 20p13             |
| casein kinase 2 alpha 2                                                                    | 115442 | NM_00189<br>6 | 16p13.3-<br>p13.2 |
| casein kinase 2 beta                                                                       | 115441 | X57152        | 6p21.3            |
| phosphatidylinositol 3-kinase,<br>regulatory subunit, polypeptide 1 (p85,<br>alpha)/PIK3R1 | 171833 | M61906        | 5q13              |
| phosphatidylinositol 3-kinase,<br>regulatory subunit, polypeptide 2 (p85,<br>beta)/PIK3R2  | 603157 | NM_00502<br>7 | 19q13.2-<br>q13.4 |
| phosphatidylinositol 3-kinase,<br>regulatory subunit, polypeptide 3 (p55,<br>gamma)/PIK3R3 | *****  | NM_00362<br>9 | *****             |
| phosphoinositide-3-kinase, catalytic,<br>alpha polypeptide/PIK3CA                          | 171834 | NM_00621<br>8 | 3q26.3            |
| phosphoinositide-3-kinase, catalytic,<br>beta polypeptide/PIK3CB                           | 602925 | NM_00621<br>9 | *****             |
| phosphatidylinositol 3-kinase,<br>catalytic, delta polypeptide/PIK3CD                      | 602839 | NM_00502<br>6 | 1p36.2            |
| phosphatidylinositol 3-kinase,<br>catalytic, gamma polypeptide/PIK3CG                      | 601232 | NM_00264<br>9 | *****             |
| peptidyl-prolyl isomerase<br>A/cyclophilin A/PPIA                                          | 123840 | Y00052        | 7p13              |
| peptidyl-prolyl isomerase<br>B/cyclophilin B/PPIB                                          | 123841 | M60857        | chr. 15           |

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| <b>Cyclophilins</b> | <b>Biosynthesis</b> | peptidyl-prolyl isomerase<br>C/cyclophilin C/PPIC                                    | 123842 | S71018    | *****        |
|                     |                     | peptidyl-prolyl isomerase<br>D/cyclophilin D/PPID                                    | 601753 | NM_005038 | 4q31.3       |
|                     |                     | peptidyl-prolyl isomerase<br>E/cyclophilin E/PPIE                                    | *****  | NM_006112 | *****        |
|                     |                     | peptidyl-prolyl isomerase-like/PPIL1                                                 | 601301 | AF090992  | 6p21.1       |
|                     | <b>Receptors</b>    | FK506 binding protein<br>1A/immunophilin/FKBP1A                                      | 186945 | NM_000801 | 20p13        |
|                     |                     | FK506 binding protein<br>2/immunophilin/FKBP2                                        | 186946 | NM_004470 | 1q13.1-q13.3 |
|                     |                     | FK506 binding protein<br>4/immunophilin/FKBP4                                        | 600611 | NM_002014 | *****        |
|                     |                     | FK506 binding protein<br>5/immunophilin/FKBP5                                        | 602623 | NM_004117 | *****        |
|                     |                     | calcium modulating cyclophilin<br>ligand/CALMLG                                      | 601118 | NM_001745 | 5q23         |
|                     |                     | protein phosphatase 3, catalytic<br>subunit, alpha isoform/calcineurin<br>A/B/C/D    | 114105 | M29550    | 4q21-q24     |
| <b>Response</b>     |                     | protein phosphatase 3, catalytic<br>subunit, beta isoform/calcineurin<br>A/B/C/D     | 114106 | M30773    | 10q21-q22    |
|                     |                     | protein phosphatase 3, catalytic<br>subunit, gamma isoform/calcineurin<br>A/B/C/D    | 114107 | NM_005605 | Chr.8        |
|                     |                     | protein phosphatase 3, regulatory<br>subunit B, alpha isoform/calcineurin<br>A/B/C/D | 601302 | *****     | 2p16-p15     |
|                     |                     | calmodulin 1/CALM1                                                                   | 114180 | AH005370  | 14q24-q31    |
|                     |                     | calmodulin 2/CALM2                                                                   | 114182 | NM_001743 | 2p21.3-p21.1 |
|                     |                     | calmodulin 3/CALM3                                                                   | 114183 | NM_005184 | 9q13.2-q13.3 |

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| Non-Cytokine Mediated Immune Regulation        | Biosynthesis                                                            | cytochrome P450, subfamily XXI (steroid 21-hydroxylase)/CYP21                       | 201910                                                                       | M13936    | 6p21.3    |            |
|                                                |                                                                         | cytochrome P450, subfamily XIB (steroid 18-beta-hydroxylase), polypeptide 2/CYP11B2 | 124080                                                                       | NM_000498 | 8q21      |            |
|                                                |                                                                         | cytochrome P450, subfamily XIB (steroid 11-beta-hydroxylase), polypeptide 1/CYP11B1 | 202010                                                                       | NM_000497 | 8q21      |            |
|                                                | Receptors and Signaling                                                 | Corticosteroids                                                                     | nuclear receptor subfamily 3, group C, member 1/NR3C1                        | 138040    | NM_000176 | 5q31       |
|                                                |                                                                         |                                                                                     | melanocortin 2 receptor/ACTH receptor/MC2R                                   | 202200    | NM_000529 | 18p11.2    |
|                                                |                                                                         |                                                                                     | mineralocorticoid receptor/MCR/nuclear receptor subfamily 3, group C, member | 600983    | NM_000901 | 4q31.1     |
|                                                |                                                                         |                                                                                     | heat shock 70kD protein 1/HSPA1A                                             | 140550    | NM_005345 | 6p21.3     |
|                                                |                                                                         |                                                                                     | heat shock 70kD protein-like 1/HSPA1L                                        | 140559    | NM_005527 | 6p21.3     |
|                                                |                                                                         |                                                                                     | heat shock 70kD protein 1/HSPA1B                                             | 603012    | NM_005346 | 6p21.3     |
|                                                |                                                                         |                                                                                     | heat shock 90-kD protein 1, alpha subunit/HSPCA                              | 140571    | *****     | 1q21.2-q22 |
| heat shock 90-kD protein 1, beta subunit/HSPCB |                                                                         |                                                                                     | 140572                                                                       | J04988    | 6p12      |            |
| FK506-binding protein 4 (59kD)/FKBP4           |                                                                         |                                                                                     | 600611                                                                       | NM_002014 | *****     |            |
|                                                |                                                                         |                                                                                     | corticosteroid binding globulin precursor/CBG                                | 122500    | NM_001756 | 14q32.1    |
|                                                | hydroxy-D-5-steroid dehydrogenase, 3b- and steroid D-isomerase 2/HSD3B2 | 201810                                                                              | NM_000198                                                                    | 1p13.1    |           |            |

|                   |                                                                                        |        |            |               |
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| <b>Metabolism</b> | UDP glycosyltransferase 1/UGT1                                                         | 191740 | NM_001072  | Chr. 12       |
|                   | UDP glycosyltransferase family 2, member B4/UGT2B4                                     | 600067 | NM_001073  | 4q13          |
|                   | UDP glycosyltransferase family 2, member B7/UGT2B7                                     | 600068 | NM_001074  | 1q14          |
|                   | UDP glycosyltransferase 2 family, polypeptide B11/UGT2B11                              | 603064 | NM_001073  | *****         |
|                   | UDP glycosyltransferase family 2, member B15/UGT2B15                                   | 600069 | NM_001076  | 4q13          |
|                   | UDP glycosyltransferase family 2, member B17/UGT2B17                                   | 601903 | NM_001077  | 1q14          |
|                   | Dehydroepiandrosterone (DHEA)-preferring sulfotransferase, family 2A, member 1/SULT2A1 | 125263 | NM_003167  | 19q13.3       |
|                   | estrogen-preferring                                                                    | 600043 | NM_005420  | 4q13.1        |
|                   | vitamin D (1,25- dihydroxyvitamin D3) receptor/VDR                                     | 601769 | NM_000376  | 12q12-q14     |
|                   | Retinoic acid receptor, alpha/RARA                                                     | 180240 | NM_0000964 | 17q12         |
| <b>Vitamin D</b>  | <b>Retinoic Acid</b>                                                                   | 180220 | NM_0000965 | 3p24          |
|                   |                                                                                        | 180190 | M57707     | 12q13         |
| <b>Receptors</b>  | Retinoic acid receptor, gamma/RARG                                                     | 186940 | X87579     | 12pter-p12    |
|                   | T-cell antigen CD4/LEU3/CD4                                                            |        | NM_006725  | Chr.11        |
|                   | T-cell antigen CD6/T-cell differentiation antigen/CD6                                  | 186720 | X04391     | 11q13         |
|                   | lymphocyte antigen CD5/LEU1/CD5                                                        | 153340 | NM_006137  | 17q25.2-q25.3 |
|                   | thymocyte antigen CD7/Tp41/CD7                                                         | 186820 |            |               |

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|--------|------------------------------------------------------------------------------|--------|-----------|-----------|
| T-Cell | lymphocyte antigen CD19/B-lymphocyte antigen/CD19                            | 107265 | X13312    | 16p11.2   |
|        | B-lymphocyte antigen CD80 (CD28 antigen ligand 1, B7-1 antigen)/CD80         | 112203 | NM_005191 | 3q21      |
|        | CD86 antigen (CD28 antigen ligand 2, B7-2 antigen)/CD86                      | 601020 | NM_006889 | 3q21      |
|        | T-cell antigen CD28 (Tp44)/CD28                                              | 186760 | NM_006139 | 2q33-q34  |
|        | T-cell antigen receptor, beta subunit/TCRB                                   | 186930 | AF011643  | 7q35      |
|        | CD3G antigen, gamma polypeptide (TiT3 complex)/CD3G                          | 186740 | NM_000073 | 11q23     |
|        | CD3D antigen, delta polypeptide (TiT3 complex)/CD3D                          | 186790 | NM_000073 | 11q23     |
|        | CD3E antigen, epsilon polypeptide (TiT3 complex)/CD3E                        | 186830 | NM_000073 | 11q23     |
|        | CD3Z antigen, zeta polypeptide (TiT3 complex)/CD3Z                           | 186780 | NM_000073 | 1q22-q23  |
|        | leukocyte common antigen                                                     | 151460 | M23492    | 1q31-q32  |
|        | T-cell antigen CD69/p60/CD69                                                 | 107273 | NM_001781 | 12p13-p12 |
|        | lymphoblast antigen CD38/ADP-ribose cyclase/cyclic ADP-ribose hydrolase/CD38 | 107270 | NM_001775 | 4p15      |
|        | lymphoblast antigen CD39/vascular ATP diphosphohydrolase/CD39                | 601752 | NM_001776 | 10q24     |
|        | lymphocyte antigen CD73/5' nucleotidase/NT5/ CD73                            | 129190 | NM_002526 | 6q14-q21  |
|        | Receptors                                                                    |        |           |           |

**Activation,  
Differentiation,  
and  
Proliferation**  
(excluding  
genes from  
cytokine  
section  
above)

|                                                                                                     |        |               |                  |
|-----------------------------------------------------------------------------------------------------|--------|---------------|------------------|
| leukocyte antigen CD23/low-affinity<br>receptor II for Fc portion of<br>IgE/FCER2/CD23              | 151445 | NM_00200<br>2 | 19p13.3          |
| macrophage antigen CD 64/high-<br>affinity receptor IA for Fc fragment of<br>IgG/FCGR1A             | 146760 | Y10206        | 1q21.2-<br>q21.3 |
| lymphocyte antigen CD57/LEU7/CD57                                                                   | 151290 | *****         | Chr.11           |
| lymphocyte function-associated<br>antigen, type 3/LAF3/LEU7/CD58                                    | 153420 | NM_00177<br>9 | 1p13             |
| lymphocyte antigen CD45/protein<br>tyrosine phosphatase, receptor type, c<br>polypeptide/PTPRC/CD45 | 151460 | NM_00283<br>8 | 1q31-q32         |
| T-cell antigen receptor, gamma<br>subunit/TCRG                                                      | 186970 | M17325        | 7p15-p14         |
| T-cell antigen receptor, delta<br>subunit/TCRD                                                      | 186810 | L36384        | 14q11.2          |
| T-cell antigen CD8, alpha polypeptide<br>(p32)/CD8A                                                 | 186910 | NM_00176<br>8 | 2p12             |
| T-cell antigen CD8, beta<br>polypeptide/CD8B                                                        | 186730 | AH003859      | 2p12             |
| T-cell antigen CD28 (Tp44)/CD28                                                                     | 186760 | NM_00613<br>9 | 2q33-q34         |
| cytotoxic T-lymphocyte-associated<br>4/CTLA4                                                        | 123890 | L15006        | 2q33             |
| T-cell antigen receptor, alpha<br>subunit/TCRA                                                      | 186880 | Z24457        | 14q11.2          |
| CD89 antigen/receptor for Fc fragment<br>of IgA/FCAR/CD89                                           | 147045 | NM_00200<br>0 | 19q13.4          |
| T-cell activation antigen p250/TP250                                                                | 186710 | *****         | 11pter-<br>p11.2 |

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| <b>Signaling</b>                                                                             | signaling lymphocytic activation molecule/SLAM                                        | 603492 | NM_003037 | *****       |
|                                                                                              | T cell receptor-associated protein tyrosine kinase ZAP-70/ZAP70                       | 176947 | S69911    | 2q12        |
|                                                                                              | v-mos Moloney murine sarcoma viral oncogene homolog/MOS                               | 190060 | NM_005372 | 8q11        |
|                                                                                              | IL2-inducible T-cell kinase/ITK/T-cell tyrosine kinase EMT/EMT                        | 186973 | NM_005546 | 5q32        |
|                                                                                              | mature T-cell proliferation 1/MTCPI                                                   | 300116 | Z24459    | Xq28        |
|                                                                                              | lymphocyte-specific protein tyrosine kinase/LCK                                       | 153390 | NM_005356 | 1p35-p34.3  |
|                                                                                              | B-cell antigen CD20/B-lymphocyte differentiation antigen B1/CD20                      | 112210 | AH003353  | 11q13       |
|                                                                                              | B-cell antigen CD72/CD72                                                              | 107272 | NM_001782 | 9p          |
|                                                                                              | macrophage protein 1/NRAMP1/solute carrier family 11, member 1/SLC11A2                | 600266 | AH002806  | 2q35        |
|                                                                                              | macrophage protein 2/NRAMP2/solute carrier family 11, member 2/SLC11A2                | 600523 | AB015355  | 12q13       |
| <b>B-Cell Activation, Differentiation, and Proliferation (excluding genes from cytokine)</b> | T-lymphocyte antigen CDW52 (CAMPATH-1 antigen)/CDW52                                  | 114280 | NM_001803 | *****       |
|                                                                                              | B-cell antigen CD22/CD22                                                              | 107266 | NM_001771 | 19q13.1     |
|                                                                                              | B-cell antigen CD24/CD24                                                              | 600074 | X69397    | 6q21        |
|                                                                                              | B-cell antigen CD40/tumor necrosis factor receptor superfamily, member 5/CD40/TNFRSF5 | 109535 | NM_001250 | 20q12-q13.2 |
|                                                                                              |                                                                                       |        |           |             |
| <b>Receptors</b>                                                                             |                                                                                       |        |           |             |
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| <i>section<br/>above)</i>                                                                                                          | leukocyte antigen CD156/disintegrin<br>and metalloprotease domain<br>8/ADAM8/CD156             | 602267 | NM_00110<br>9 | 10q26.3           |
|                                                                                                                                    | platelet antigen CD151/platelet-<br>endothelial cell tetraspan antigen<br>3/PETA3/CD151        | 602243 | NM_00435<br>7 | 11p15.5           |
|                                                                                                                                    | IIA for Fc fragment of<br>IgG/FCGR2A/CD32                                                      | 146790 | NM_00400<br>1 | 1q21-q23          |
|                                                                                                                                    | activated leucocyte cell adhesion<br>molecule/CD6 ligand/ALCAM                                 | 601662 | NM_00162<br>7 | 3q13.1-<br>q13.2  |
|                                                                                                                                    | regulator of G-protein signaling<br>1/RGS1                                                     | 600323 | NM_00292<br>2 | 1q31              |
| <b>Growth<br/>Factors</b>                                                                                                          | macrophage-specific colony-<br>stimulating factor/CSF1                                         | 120420 | AH005300      | 1p21-p13          |
|                                                                                                                                    | granulocyte-macrophage colony<br>stimulating factor 2/CSF2                                     | 138960 | NM_00075<br>8 | 5q31.1            |
|                                                                                                                                    | granulocyte colony stimulating factor<br>3/CSF3                                                | 138970 | NM_00075<br>9 | 17q11.2-<br>q12   |
|                                                                                                                                    | colony stimulating factor 1<br>receptor/CSFR1                                                  | 164770 | U63963        | 5q33.2-<br>q33.3  |
|                                                                                                                                    | granulocyte-macrophage colony<br>stimulating factor 2 receptor, alpha, Y<br>chromosomal/CSF2RY | 425000 | *****         | Yp11              |
| <b>Myeloid<br/>Progenitor<br/>Cell<br/>Differentiation<br/>on and<br/>Proliferation<br/>(excluding<br/>genes from<br/>cytokine</b> | granulocyte-macrophage colony<br>stimulating factor 2 receptor, alpha,<br>low-affinity/CSF2RA  | 306250 | NM_00614<br>0 | Xp22.32           |
|                                                                                                                                    | granulocyte-macrophage colony<br>stimulating factor 2 receptor,<br>beta/CSF2RB                 | 138981 | U18373        | 22q12.2-<br>q13.1 |
| <b>Receptors</b>                                                                                                                   |                                                                                                |        |               |                   |



|                   |           |                                                             |        |               |                   |
|-------------------|-----------|-------------------------------------------------------------|--------|---------------|-------------------|
| section<br>above) | Signaling | CCAAT/enhancer binding protein<br>(C/EBP), beta/CEBPB       | 189965 | NM_00519<br>4 | 20q13.1           |
|                   |           | CCAAT/enhancer binding protein<br>(C/EBP), epsilon/CEBPE    | 600749 | NM_00180<br>5 | 14q11.2           |
|                   |           | flt3 ligand/FMS-related tyrosine<br>kinase 3 ligand/FLT3LG  | 600007 | U03858        | 19q13.3           |
|                   |           | FMS-related tyrosine kinase 3/FLT3                          | 136351 | NM_00411<br>9 | 13q12             |
|                   |           | myeloid differentiation primary<br>response gene (88)/MYD88 | 602170 | NM_00246<br>8 | 3p22-p21.3        |
|                   |           | BCL2                                                        | 151430 | M13994        | 18q21.3           |
|                   |           | BCL-X/BCLX                                                  | 600039 | Z23115        | *****             |
|                   |           | BCL2 associated protein/BAX                                 | 600040 | L22473        | 19q13.3-<br>q13.4 |
|                   |           | BCL2-antagonist/killer 1/BAK1                               | 600516 | NM_00118<br>8 | 6p21.3-<br>p21.2  |
|                   |           | BCL2-associated athanogene 1/BAG1                           | 601497 | NM_00432<br>3 | 9p12              |
|                   |           | BCL2-associated athanogene 2/BAG2                           | 603882 | NM_00428<br>2 | *****             |
|                   |           | BCL2-associated athanogene 3/BAG3                           | 603883 | AF095193      | *****             |
|                   |           | BCL2-associated athanogene 4/BAG4                           | 603884 | AF095194      | *****             |
|                   |           | BCL2-associated athanogene 5/BAG5                           | 603885 | AF095195      | *****             |
|                   |           | BCL-X/BCL-2 binding protein/BAD                             | 603167 | AF021792      | *****             |
|                   |           | BCL2-like 1/BCL2L1                                          | 600039 | NM_00119<br>1 | *****             |
|                   |           | BCL2-like 2/BCL2L2                                          | 601931 | NM_00405<br>0 | 14q11.2-<br>q12   |
|                   |           | BCL2-like 11 (apoptosis<br>facilitator)/BCL2L11             | 603827 | NM_00653<br>8 | *****             |

|                                                          |        |               |                     |
|----------------------------------------------------------|--------|---------------|---------------------|
| BCL2-related protein A1/BCL2A1                           | 601056 | Y09397        | 15q24.3             |
| BCL2-interacting protein<br>harikari/HRK                 | 603447 | NM_00380<br>6 | *****               |
| Bcl-2 interacting killer/BIK                             | 603392 | U34584        | *****               |
| tumor protein p53/TP53                                   | 191170 | X02469        | 17p13.1             |
| superfamily, member<br>6/FAS/TNFRSF6                     | 134637 | NM_00004<br>3 | 10q24.1             |
| nuclear factor kappa-B DNA binding<br>subunit 1/NFKB1    | 164011 | M58603        | 4q23-q24            |
| nuclear factor kappa-B DNA binding<br>subunit 2/NFKB2    | 164012 | NM_00250<br>2 | 10q24               |
| apoptosis-related cysteine protease<br>1/caspase 1/CASP1 | 147678 | L27475        | 11q22.2-<br>q22.3   |
| apoptosis-related cysteine protease<br>1/caspase 1/CASP2 | 600639 | *****         | 7q35                |
| apoptosis-related cysteine protease<br>1/caspase 1/CASP3 | 600636 | NM_00434<br>6 | 4q35, 4q33<br>q35.1 |
| apoptosis-related cysteine protease<br>1/caspase 1/CASP4 | 602664 | NM_00434<br>7 | 11q22.2-<br>q22.3   |
| apoptosis-related cysteine protease<br>1/caspase 1/CASP5 | 602665 | NM_00434<br>7 | 11q22.2-<br>q22.3   |
| apoptosis-related cysteine protease<br>1/caspase 1/CASP6 | 601532 | NM_00122<br>6 | 4q25-q25            |
| apoptosis-related cysteine protease<br>1/caspase 1/CASP7 | 601761 | NM_00122<br>7 | 10q25.1-<br>q25.2   |
| apoptosis-related cysteine protease<br>1/caspase 1/CASP8 | 601763 | NM_00122<br>8 | 2q33-q34            |
| apoptosis-related cysteine protease<br>1/caspase 1/CASP9 | 602234 | *****         | *****               |

### Apoptosis

**Apoptosis**  
(additional  
genes in  
Oncology)

**Cell-  
Mediated  
Inflammation**

|                                                                                           |        |               |           |
|-------------------------------------------------------------------------------------------|--------|---------------|-----------|
| apoptosis-related cysteine protease<br>1/caspase 1/CASP10                                 | 601762 | NM_00123<br>0 | 2q33-q34  |
| apoptosis-related cysteine protease<br>1/caspase 1/CASP13                                 | 603653 | NM_00372<br>3 | *****     |
| ADP-ribosyltransferase (NAD <sup>+</sup> ; poly<br>(ADP-ribose)<br>polymerase)/PARP/ADPRT | 173870 | NM_00161<br>8 | 1q42      |
| poly (ADP-ribose)<br>glycohydrolase/PARG                                                  | 603501 | NM_00363<br>1 | 10q11.23  |
| lymphocyte antigen CD11A/integrin,<br>alpha-L/CD11A/ITGAL                                 | 153370 | NM_00220<br>9 | 16p11.2   |
| lymphocyte antigen CD11B/integrin,<br>alpha-M/CD11B/ITGAM                                 | 120980 | NM_00063<br>2 | 16p11.2   |
| lymphocyte antigen CD11C/integrin,<br>alpha-X/CD11C/ITGAX                                 | 151510 | NM_00088<br>7 | 16p11.2   |
| lymphocyte antigen CD11D/integrin,<br>alpha-D/CD11D/ITGAD                                 | 602453 | NM_00535<br>3 | 16p11.2   |
| antigen CD51/integrin, alpha-<br>V/vitronectin receptor/CD51/ITGAV                        | 193210 | NM_00221<br>0 | 2q31-q32  |
| integrin, alpha 1/ITGA1                                                                   | 192968 | *****         | Chr.5     |
| integrin, alpha 2/ITGA2                                                                   | 192974 | NM_00220<br>3 | 5q23-q31  |
| integrin, alpha 3/ITGA3                                                                   | *****  | NM_00550<br>1 | *****     |
| integrin, alpha 4/ITGA4                                                                   | 192975 | NM_00088<br>5 | 2q31-q32  |
| integrin, alpha5/fibronectin receptor,<br>alpha subunit/FNRA/ITGA5                        | 135620 | NM_00220<br>5 | 12q11-q13 |
| integrin, alpha 6/ITGA6                                                                   | 147556 | NM_00021<br>0 | Chr.2     |

|                  |                                                                                         |        |           |               |
|------------------|-----------------------------------------------------------------------------------------|--------|-----------|---------------|
| <b>Integrins</b> | integrin, alpha 7/ITGA7                                                                 | 600536 | NM_002206 | 12q13         |
|                  | integrin, alpha 8/ITGA8                                                                 | 604063 | L36531    | *****         |
|                  | integrin, alpha 9/ITGA9                                                                 | 603963 | L24158    | 3p21.3        |
|                  | integrin, alpha 10/ITGA10                                                               | 604042 | NM_003637 | *****         |
|                  | antigen CD29/integrin, beta-1/CD29/ITGB1                                                | 135630 | NM_002211 | 10p11.2       |
|                  | leukocyte antigen CD18/integrin beta chain, beta 2/CD18/ITGB2                           | 600065 | NM_000211 | 21q22.3       |
|                  | platelet antigen CD61/integrin, beta-3/CD61/ITGB3                                       | 173470 | NM_000212 | 17q21.32      |
|                  | integrin, beta 5/ITGB5                                                                  | 147561 | NM_002213 | *****         |
|                  | integrin, beta 6/ITGB6                                                                  | 147558 | NM_000888 | Chr.2         |
|                  | integrin, beta 7/ITGB7                                                                  | 147559 | NM_000889 | 12q13.13      |
|                  | integrin, beta-like 1 (with EGF-like repeat domains)/ITGBL1                             | 604234 | NM_004791 | 13q33         |
|                  | erythrocyte antigen CD47/Rh-related antigen, integrin-associated signal transducer/CD47 | 601028 | NM_001777 | 3q13.1-q13.2  |
|                  | integrin-linked kinase/ILK                                                              | 602366 | NM_004517 | 11p15.5-p15.4 |
|                  | selectin E/endothelial adhesion molecule 1/ELAM1/SELE                                   | 131210 | NM_000450 | 1q23-q25      |
| <b>Selectins</b> | granulocyte antigen CD62/platelet alpha-granule membrane protein/selectin P/CD62/SELP   | 173610 | NM_003005 | 1q23-q25      |

|                              |                                                                                  |        |           |              |
|------------------------------|----------------------------------------------------------------------------------|--------|-----------|--------------|
| Adhesion<br>and<br>Migration | selectin L/lymphocyte adhesion molecule 1/LAM1/SELL                              | 153240 | NM_000655 | 1q23-q25     |
|                              | T-cell antigen CD8, alpha polypeptide (p32)/LEU2/CD8A                            | 186910 | NM_001768 | 2p12         |
|                              | T-cell antigen CD8, beta polypeptide/CD8B                                        | 186730 | AH003859  | 2p12         |
|                              | leukocyte antigen CD9/MIC3/CD9                                                   | 143030 | NM_001769 | 12p13        |
|                              | activated leucocyte cell adhesion molecule/CD6 ligand/ALCAM                      | 601662 | NM_001627 | 3q13.1-q13.2 |
|                              | mucosal addressin cell adhesion molecule-1/MACAM1                                | 102670 | NM_007164 | 19p13.3      |
|                              | platelet antigen CD151/platelet-endothelial cell tetraspan antigen 3/PETA3/CD151 | 602243 | NM_004357 | 11p15.5      |
|                              | CD36/thrombospondin receptor/platelet collagen                                   | 173510 | NM_000072 | 7q11.2       |
|                              | leukocyte antigen CD37/CD37                                                      | 151523 | NM_001774 | 19p13-q13.4  |
|                              | platelet antigen CD31/platelet-endothelial cell adhesion molecule 1/PECAM1/CD31  | 173445 | NM_000442 | 17q23        |
|                              | T-cell antigen CD26/dipeptidylpeptidase IV/CD26                                  | 102720 | NM_001935 | 2q23         |
|                              | lymphocyte antigen CD44/hermes antigen/CD44                                      | 107269 | AF098641  | 11pter-p13   |
|                              | B-cell antigen CD 48/B-cell activation marker/BCM1/BLAST1                        | 109530 | NM_001778 | 1q21.3-q22   |
|                              | leukocyte antigen CD53/tetraspan antigen/CD53                                    | 151525 | AJ243474  | 1p21-p13.3   |

**Other  
Adhesion  
Molecules**

|                                                                                            |        |           |               |
|--------------------------------------------------------------------------------------------|--------|-----------|---------------|
| B-cell antigen CD54/intercellular adhesion molecule 1/ICAM1/CD54                           | 147840 | NM_000201 | 19p13.3-p13.2 |
| intercellular adhesion molecule 2/ICAM2                                                    | 146630 | NM_000873 | 17q23-q25     |
| intercellular adhesion molecule 3/ICAM3                                                    | 146631 | NM_002162 | 19p13.3-p13.2 |
| myeloid antigen CD33/p67/CD33                                                              | 159590 | NM_001772 | 19q13.3-q13.4 |
| granulocyte antigen CD66/biliary glycoprotein/CD66                                         | 109770 | NM_001712 | 19q13.2       |
| leukocyte antigen CD81/target of antiproliferative antibody 1/TAPAI/CD81                   | 186845 | NM_004356 | 11p           |
| leukocyte antigen CD82/R2/suppression of tumorigenicity 1/STES1/CD82                       | 600623 | NM_002231 | 11p11.2       |
| killer cell lectin-like receptor subfamily B, member 1/KLRB1                               | 602890 | NM_002258 | 12p13-p12     |
| killer cell lectin-like receptor subfamily C, member 1/KLRC1                               | 161555 | NM_002259 | 12p13.2-p12.3 |
| killer cell lectin-like receptor subfamily C, member 2/KLRC2                               | 602891 | NM_002260 | 12p13.2-p12.3 |
| killer cell lectin-like receptor subfamily C, member 3/KLRC3                               | 602892 | NM_002261 | 12p13.2-p12.3 |
| killer cell lectin-like receptor subfamily C, member 4/KLRC4                               | 602893 | NM_003497 | 12p13.2-p12.3 |
| killer cell antigen CD94/killer cell lectin-like receptor subfamily D, member 1/KLRD1/CD94 | 602894 | NM_002262 | 12p13.2-p12.3 |
| T-cell antigen CD99/MIC2/CD99                                                              | 313470 | NM_002414 | Xpter-p22.32  |

|                      |                                                                          |        |           |          |
|----------------------|--------------------------------------------------------------------------|--------|-----------|----------|
|                      | leukocyte antigen CD100/semaphorin 4D/SEMA4D/CD100                       | 601866 | NM_006378 | 9q22-q31 |
|                      | hematopoietic progenitor cell antigen CD34/CD34                          | 142230 | AH000040  | 1q32     |
|                      | macrophage antigen CD68/macrosialin/CD68                                 | 153634 | NM_001251 | 17p13    |
|                      | cadherin 2, N-cadherin (neuronal)/CDH2                                   | 114020 | NM_001792 | 18q11.2  |
|                      | receptor for advanced glycation end products/RAGE                        | 600214 | AJ133822  | 6p21.3   |
|                      | leukocyte antigen CD43/sialophorin/SPN/CD43                              | 182160 | NM_003123 | 16p11.2  |
|                      | vascular cell adhesion molecule 1/VCAM1                                  | 192225 | NM_001078 | 1p32-p31 |
|                      | UDP-Gal:betaGlcNAc beta 1,4-galactosyltransferase, polypeptide 1/B4GALT1 | 137060 | NM_001497 | 9p13     |
|                      | UDP-Gal:betaGlcNAc beta 1,4-galactosyltransferase, polypeptide 2/B4GALT2 | 604013 | NM_003780 | 1p33-p32 |
|                      | UDP-Gal:betaGlcNAc beta 1,4-galactosyltransferase, polypeptide 3/B4GALT3 | 604014 | NM_003779 | 1q23     |
|                      | UDP-Gal:betaGlcNAc beta 1,4-galactosyltransferase, polypeptide 4/B4GALT4 | 604015 | AF038662  | 3q13.3   |
|                      | UDP-Gal:betaGlcNAc beta 1,4-galactosyltransferase, polypeptide 5/B4GALT5 | 604016 | NM_004776 | Chr.11   |
| Glycosyltransferases | Glycosyltransferases                                                     |        |           |          |

|                                                                                           |        |           |               |
|-------------------------------------------------------------------------------------------|--------|-----------|---------------|
| UDP-Gal:betaGlcNAc beta 1,4-galactosyltransferase, polypeptide 6/B4GALT6                  | 604017 | AF038664  | 18q11         |
| myeloid antigen CD15/fucosyltransferase 4/CD15                                            | 104230 | NM_002033 | 11q21         |
| monocyte antigen CD87/plasminogen activator receptor, urokinase type/PLAUR/CD87           | 173391 | NM_002659 | 19q13         |
| lymphocyte antigen CD10/membrane metalloendopeptidase/MME/CD10                            | 120520 | NM_000902 | 3q21-q27      |
| leukocyte antigen CD13/alanyl aminopeptidase/ANPEP/CD13                                   | 151530 | NM_001150 | 15q25-q26     |
| chymase 1, mast cell/CMA1                                                                 | 118938 | NM_001836 | 14q11.2       |
| tryptase alpha/TPS1                                                                       | 191080 | NM_003293 | Chr.16        |
| matrix metalloproteinase 1 (interstitial collagenase)/MMP1                                | 120353 | NM_002421 | 11q22-q23     |
| matrix metalloproteinase-like 1/MMPL1                                                     | *****  | NM_004142 | *****         |
| matrix metalloproteinase 2 (neutrophil gelatinase)/CLG4/MMP2                              | 120360 | AH002654  | 16q13         |
| matrix metalloproteinase 3 (stromelysin 1, progelatinase)/MMP3                            | 185250 | NM_002422 | 11q23         |
| matrix metalloproteinase 8 (neutrophil collagenase)/MMP8                                  | 120355 | NM_002424 | 11q21-q22     |
| matrix metalloproteinase 9 (gelatinase B, 92kD gelatinase, 92kD type IV collagenase)/MMP9 | 120361 | NM_004994 | 10q11.2-q13.1 |
| matrix metalloproteinase 10 (stromelysin 2)/MMP10                                         | 185260 | NM_002425 | 11q22.3-q23   |

**Proteases**



**Proteases  
and  
Inhibitors**

|                                                                                                                            |        |           |                   |
|----------------------------------------------------------------------------------------------------------------------------|--------|-----------|-------------------|
| matrix metalloproteinase 11<br>(stromelysin 3)/MMP11                                                                       | 185261 | NM_005940 | 22q11.2           |
| matrix metalloproteinase 12<br>(macrophage elastase)/MMP12                                                                 | 601046 | NM_002426 | 1q22.2-q22.3      |
| matrix metalloproteinase 13<br>(collagenase 3)/MMP13                                                                       | 600108 | NM_002427 | 11q22.3           |
| matrix metalloproteinase 14<br>(membrane-inserted)/MMP14                                                                   | 600754 | NM_004995 | 14q11-q12         |
| matrix metalloproteinase 15<br>(membrane-inserted)/MMP15                                                                   | 602261 | NM_002428 | 16q13-q21         |
| matrix metalloproteinase 16<br>(membrane-inserted)/MMP16                                                                   | 602262 | NM_005941 | 8q21              |
| matrix metalloproteinase 17<br>(membrane-inserted)/MMP17                                                                   | 602285 | NM_004141 | 12q24.33          |
| matrix metalloproteinase 19/MMP19                                                                                          | 601807 | NM_002429 | 12q14             |
| matrix metalloproteinase<br>23A/MMP23A                                                                                     | 603320 | NM_004659 | 1p36.3            |
| matrix metalloproteinase<br>23B/MMP23B                                                                                     | 603321 | NM_006983 | 1p36.3            |
| matrix metalloproteinase 24<br>(membrane-inserted)/MMP24                                                                   | *****  | NM_006690 | *****             |
| tryptase beta/TPS2                                                                                                         | 191081 | NM_003294 | Chr.16            |
| tissue inhibitor of metalloproteinase<br>1/erythroid potentiating<br>activity/EPA/human collagenase<br>inhibitor/HCI/TIMP1 | 305370 | NM_003254 | Xp11.3-<br>p11.23 |
| secretory leukocyte protease inhibitor<br>(antileukoproteinase)/SLPI                                                       | 107285 | NM_003064 | *****             |

**Inhibitors**

|  |  |  |                                                                                     |        |           |              |
|--|--|--|-------------------------------------------------------------------------------------|--------|-----------|--------------|
|  |  |  | monocyte/neutrophil elastase inhibitor/ELANH2                                       | 130135 | M93056    | 6pter-p24    |
|  |  |  | alpha-1-microglobulin/bikunin precursor/AMBP                                        | 176870 | NM_001633 | 9q32-q33     |
|  |  |  | alpha-2-macroglobulin/A2M                                                           | 103950 | NM_000014 | 2p13.3-p12.3 |
|  |  |  | CD36/thrombospondin receptor/platelet collagen                                      | 173510 | NM_000072 | 7q11.2       |
|  |  |  | CD36 antigen (collagen type I receptor, thrombospondin receptor)-like 1/CD36L1/SRB1 | 601040 | NM_005505 | Chr. 12      |
|  |  |  | CD5 antigen-like (scavenger receptor cysteine rich family)/CD5L                     | 602592 | NM_005894 | 1q21-q23     |
|  |  |  | acetyl LDL receptor/scavenger receptor expressed by endothelial                     | *****  | NM_003693 | *****        |
|  |  |  | macrophage scavenger receptor 1/MSR1                                                | 153622 | NM_002445 | 8p22         |
|  |  |  | macrophage scavenger receptor 1-like/MSRL1                                          | 602728 | *****     | 8p21         |
|  |  |  | mannose receptor, C type 1/MRC1                                                     | 153618 | NM_002438 | 10p13        |
|  |  |  | endocytic receptor (macrophage mannose receptor family) (KIAA0709)                  | *****  | NM_006039 | *****        |
|  |  |  | toll-like receptor 1/TLR1                                                           | 601194 | NM_003263 | 4p14         |
|  |  |  | toll-like receptor 2/TLR2                                                           | 603028 | NM_003264 | 4q32         |
|  |  |  | toll-like receptor 3/TLR3                                                           | 603029 | NM_003265 | 4q35         |
|  |  |  | toll-like receptor 4/TLR4                                                           | 603030 | NM_003266 | 9q32-q33     |
|  |  |  | toll-like receptor 5/TLR5                                                           | 603031 | NM_006068 | 1q41-q42     |
|  |  |  | collectin 34                                                                        | *****  | AB002631  | *****        |
|  |  |  | liver collectin 1/CL-L1                                                             | *****  | NM_006438 | *****        |
|  |  |  | collectin receptor/complement component C1q receptor/C1QR                           | 120577 | *****     |              |
|  |  |  |                                                                                     |        |           |              |

Cell-Mediated Pathogen Defense

Phagocytosis of Pathogens

Scavenger Receptors

|                             |                                       |                                                            |        |           |              |
|-----------------------------|---------------------------------------|------------------------------------------------------------|--------|-----------|--------------|
|                             |                                       | surfactant, pulmonary-associated protein D/SFTPD           | 178635 | NM_003019 | 10q23.3      |
|                             |                                       | surfactant, pulmonary-associated protein A1/SFTPA1         | 178630 | NM_005411 | 0q22.2-q23.1 |
| Immunoglobulin Light Chains | Kappa Light Chain                     | immunoglobulin K light chain constant region locus/IGKC    | 147200 | *****     | 2p12         |
|                             |                                       | immunoglobulin K light chain variable region locus/IGKV    | 146980 | K01322    | 2p12         |
|                             |                                       | immunoglobulin K light chain joining region locus/IGKJ     | 146970 | *****     | 2p12         |
|                             | Lambda Light Chain                    | immunoglobulin L light chain constant region locus/IGLC1   | 147220 | NM_006146 | 22q11.2      |
|                             |                                       | immunoglobulin L light chain joining region locus/IGLJ     | 147230 | NM_006146 | 22q11.2      |
|                             |                                       | immunoglobulin L light chain variable region locus/IGLJ    | 147240 | NM_006146 | 22q11.2      |
|                             | IgA Heavy Chain Constant Region       | immunoglobulin A heavy chain constant region locus 1/IGHA1 | 146900 | *****     | 14q32.33     |
|                             |                                       | immunoglobulin A heavy chain constant region locus 2/IGHA2 | 147000 | *****     | 14q32.33     |
|                             | IgD Heavy Chain Constant Region Locus |                                                            |        |           |              |
|                             |                                       | immunoglobulin D heavy chain constant region locus/IGHD    | 147170 | *****     | 14q32.33     |

|                                    |                                              |                                                            |        |        |           |
|------------------------------------|----------------------------------------------|------------------------------------------------------------|--------|--------|-----------|
| <b>Immunoglobulin Heavy Chains</b> | <b>IgE Heavy Chain Constant Region Locus</b> | immunoglobulin E heavy chain constant region locus/IGHE    | 147180 | *****  | 14q32.33  |
|                                    | <b>IgG Heavy Chain Constant Region Locus</b> | immunoglobulin G heavy chain constant region locus 1/IGHG1 | 147100 | *****  | 14q32.33  |
|                                    |                                              | immunoglobulin G heavy chain constant region locus 2/IGHG2 | 147110 | *****  | 14q32.33  |
|                                    |                                              | immunoglobulin G heavy chain constant region locus 3/IGHG3 | 147120 | *****  | 14q32.33  |
|                                    |                                              | immunoglobulin G heavy chain constant region locus 4/IGHG4 | 147130 | *****  | 14q32.33  |
| <b>Immunoglobulin Light Chains</b> | <b>IgM Heavy Chain Constant Region Locus</b> | immunoglobulin M heavy chain constant region locus/IGHM    | 147020 | *****  | 14q32.33  |
|                                    | <b>Heavy Chain Variable Region Locus</b>     | immunoglobulin heavy chain variable region locus 1/IGHV1   | 147070 | X92279 | 14q32.33  |
|                                    |                                              | immunoglobulin heavy chain variable region locus 2/IGHV2   | 600949 | *****  | 16p11     |
|                                    | <b>Heavy Chain Diversity Region Locus</b>    | immunoglobulin heavy chain diversity region locus 1/IGHDY1 | 146910 | X97051 | 14q32.33  |
|                                    |                                              | immunoglobulin heavy chain diversity region locus 2/IGHDY2 | 146990 | L25544 | 15q11-q12 |

| Immunoglobulin Gene Rearrangement | Heavy Chain Joining Region Locus | immunoglobulin heavy chain joining region locus/IGHJ                               | 147010 | *****     | 14q32.33      |
|-----------------------------------|----------------------------------|------------------------------------------------------------------------------------|--------|-----------|---------------|
|                                   | Signaling                        | recombination activating gene 1/RAG1                                               | 179615 | NM_000448 | 11p13         |
|                                   |                                  | recombination activating gene 2/RAG2                                               | 179616 | M94633    | 11p13         |
|                                   |                                  | immunoglobulin kappa J region recombination signal binding protein/RBPJK/IGKJRB1   | 147183 | L07872    | 9p13-p12      |
|                                   |                                  | Bruton agammaglobulinemia tyrosine kinase/BTK                                      | 300300 | NM_000061 | Xq21.3-q22    |
|                                   |                                  | interleukin 7 receptor/IL7R                                                        | 146661 | NM_002185 | 5p13          |
|                                   |                                  | interferon-gamma receptor 1/IFNGR1                                                 | 107470 | NM_000416 | 6q23-q24      |
|                                   |                                  | interferon-gamma receptor 2/IFNGR2                                                 | 147569 | NM_005534 | 21q22.1-q22.2 |
|                                   |                                  | interleukin 4 receptor precursor/IL4R                                              | 147781 | NM_000418 | 16p12.1-p11.2 |
|                                   |                                  | interleukin 4 receptor precursor/IL4R                                              | 147781 | NM_000418 | 16p12.1-p11.2 |
|                                   |                                  | ligase I, DNA, ATP-dependent/LIG1                                                  | 126391 | NM_000234 | 19q13.2-q13.3 |
|                                   |                                  | ligase IV, DNA, ATP-dependent/LIG4                                                 | 601837 | NM_002312 | 13q22-q34     |
|                                   | Recombination                    | X-ray repair, complementing defect in Chinese hamster/Ku antigen, 80 kD/KU80/XRCC5 | 194364 | *****     | 2q35          |

|  |                                                                                            |        |               |                   |
|--|--------------------------------------------------------------------------------------------|--------|---------------|-------------------|
|  | thyroid autoantigen, 70<br>kD/KU7C/G22P1                                                   | 152690 | NM_00146<br>9 | 22q11-q13         |
|  | nuclear factor kappa-B DNA binding<br>subunit 1/NFKB1                                      | 164011 | M58603        | 4q23-q24          |
|  | nuclear factor kappa-B DNA binding<br>subunit 2/NFKB2                                      | 164012 | NM_00250<br>2 | 10q24             |
|  | nuclear factor kappa-B subunit<br>3/NFKB3                                                  | 164014 | Z22949        | 11q12-q13         |
|  | nuclear factor of kappa light chain<br>gene enhancer in B cells, inhibitor<br>alpha/NFKBIA | 164008 | *****         | 14q13             |
|  | nuclear factor of kappa light chain<br>gene enhancer in B cells, inhibitor<br>beta/NFKBIB  | 603258 | NM_00250<br>3 | 8p11.2            |
|  | YY1 transcription factor/YY1                                                               | 600013 | NM_00340<br>3 | 14q               |
|  | immunoglobulin transcription factor<br>1/ITF1/transcription factor 3/TCF3                  | 147141 | *****         | 19p13.3           |
|  | immunoglobulin transcription factor<br>2/ITF2/transcription factor 4/TCF4                  | 602272 | NM_00319<br>9 | 18q21.1           |
|  | immunoglobulin mu binding protein<br>2/IGHMBP2                                             | 600502 | NM_00218<br>0 | 11q13.2-<br>q13.4 |
|  | transcription factor binding to IGHM<br>enhancer 3/TFE3                                    | 314310 | NM_00652<br>1 | Xp11.22           |
|  | homeobox protein OCT1/POU domain<br>transcription factor 2, class 1/POU2F1                 | 164175 | NM_00269<br>7 | 1q22-q23          |
|  | homeobox protein OCT2/POU domain<br>transcription factor 2, class 2/POU2F2                 | 164176 | M22596        | Chr.19            |
|  | POU domain, class 2, associating<br>factor 1/POU2AF1                                       | 601206 | NM_00623<br>5 | 11q23.1           |

Immunoglobulin Gene  
Transcription Factors

|                                  |           |                                                                                               |        |           |             |
|----------------------------------|-----------|-----------------------------------------------------------------------------------------------|--------|-----------|-------------|
|                                  |           | inhibitor of DNA binding 1, dominant negative helix-loop-helix protein/ID1                    | 600349 | NM_002165 | 20q11       |
|                                  |           | inhibitor of DNA binding 2, dominant negative helix-loop-helix protein/ID2                    | 600386 | NM_002166 | 2p25        |
| Immunoglobulin Isotype Switching | Signaling | B-cell antigen CD40/tumor necrosis factor receptor superfamily, member 5/CD40/TNFRSF5         | 109535 | NM_001250 | 20q12-q13.2 |
|                                  |           | paired box gene 5/B-cell lineage-specific activator protein/BSAP/PAX5                         | 167414 | *****     | 9p13        |
|                                  |           | lymphocyte function-associated antigen, type 3/LFA3/LEU7/CD58                                 | 153420 | NM_001779 | 1p13        |
|                                  |           | interleukin 10 receptor, alpha/IL10RA                                                         | 146933 | NM_001558 | 11q23.3     |
|                                  |           | lymphocyte antigen CD45/protein tyrosine phosphatase, receptor type, c polypeptide/PTPRC/CD45 | 151460 | NM_002838 | 1q31-q32    |
|                                  |           | prostaglandin E receptor 1, EP1 subtype/PTGER1                                                | 176802 | NM_000955 | 19p13.1     |
|                                  |           | prostaglandin E receptor 2, EP2 subtype/PTGER2                                                | 176804 | *****     | 5p13.1      |
|                                  |           | prostaglandin E receptor 3, EP3 subtype/PTGER3                                                | 176806 | NM_000957 | 1p31.2      |
|                                  |           | prostaglandin E receptor 4, EP4 subtype/PTGER4                                                | 601586 | NM_000958 | 5p13.1      |
|                                  |           | interleukin 13 receptor, alpha 1/IL13RA1                                                      | 300119 | NM_001560 | Chr.X       |
|                                  |           | interleukin receptor 13 alpha2/IL13A2                                                         | 300130 | X95302    | Xq24        |
|                                  |           | interferon-gamma receptor 1/IFNGR1                                                            | 107470 | NM_000416 | 6q23-q24    |

|                                     |                                                                                                          |        |               |                   |
|-------------------------------------|----------------------------------------------------------------------------------------------------------|--------|---------------|-------------------|
| Defense<br>Proteins and<br>Peptides | interferon-gamma receptor 2/IFNGR2                                                                       | 147569 | NM_00553<br>4 | 21q22.1-<br>q22.2 |
|                                     | interleukin 5 receptor alpha/IL5RA                                                                       | 147851 | M96652        | 3p26-p24:         |
|                                     | transforming growth factor, beta<br>receptor I (activin A receptor type II-<br>like kinase, 53kD)/TGFBRI | 190181 | NM_00461<br>2 | 9q33-q34          |
|                                     | transforming growth factor, beta<br>receptor II (70-80kD)/TGFBRII                                        | 190182 | NM_00324<br>2 | 3p22              |
|                                     | transforming growth factor, beta<br>receptor III (betaglycan,<br>300kD)/TGFBRIII                         | 600742 | NM_00324<br>3 | 1p33-p32          |
| Recombination                       | X-ray repair, complementing defect in<br>Chinese hamster/Ku antigen, 80<br>kD/KU80/XRCC5                 | 194364 | *****         | 2q35              |
|                                     | thyroid autoantigen, 70<br>kD/KU70/G22P1                                                                 | 152690 | NM_00146<br>9 | 22q11-q13         |
|                                     | complement component 1, R<br>subcomponent/C1R                                                            | 216950 | NM_00173<br>3 | 12p13             |
|                                     | complement component 1, S<br>subcomponent/C1S                                                            | 120580 | NM_00173<br>4 | 12p13             |
|                                     | complement component 1, Q<br>subcomponent, alpha<br>polypeptide/C1QA                                     | 120550 | *****         | 1p36.3-<br>p34.1  |
|                                     | complement component 1, Q<br>subcomponent, beta<br>polypeptide/C1QB                                      | 120570 | *****         | 1p36.3-<br>p34.1  |
|                                     | complement component 1, Q<br>subcomponent, gamma<br>polypeptide/C1QG                                     | 120575 | *****         | 1p36.3-<br>p34.1  |
|                                     | complement component 1, Q<br>subcomponent binding protein/C1QBP                                          | 601269 | NM_00121<br>2 | 17p13.3           |



|                                                                    |        |               |                   |
|--------------------------------------------------------------------|--------|---------------|-------------------|
| complement component 1 inhibitor<br>(angioedema, hereditary) /C1NH | 106100 | NM_00006<br>2 | 11q11-<br>q13.1   |
| complement component 2/C2                                          | 217000 | NM_00006<br>3 | 6p21.3            |
| complement component 3/C3                                          | 120700 | NM_00006<br>4 | 19p13.3-<br>p13.2 |
| complement component 4B/C4B                                        | 120820 | NM_00059<br>2 | 6p21.3            |
| complement component 5/C5                                          | 120900 | NM_00173<br>5 | 9q34.1            |
| complement component 6/C6                                          | 217050 | NM_00006<br>5 | 5p13              |
| complement component 7/C7                                          | 217070 | NM_00058<br>7 | 5p13              |
| complement component 8, alpha<br>polypeptide/C8A                   | 120950 | NM_00056<br>2 | 1p32              |
| complement component 8, beta<br>polypeptide/C8B                    | 120960 | NM_00006<br>6 | 1p32              |
| complement component 8, gamma<br>polypeptide/C8G                   | 120930 | NM_00060<br>6 | 9q34.3            |
| complement component 9/C9                                          | 120940 | NM_00173<br>7 | 5p13              |
| complement factor H/H factor 1/HF1                                 | 134370 | NM_00018<br>6 | 1q32              |
| I factor (complement)/IF                                           | 217030 | NM_00020<br>4 | 4q25              |
| decay-accelerating factor for<br>complement/DAF/CD55               | 125240 | S72858        | 1q32              |
| perforin 1/preforming protein/PRF1                                 | 170280 | NM_00504<br>1 | 10q22             |

**Classical  
Pathway**

**Complement**

|                                                                                             |                                          |           |               |
|---------------------------------------------------------------------------------------------|------------------------------------------|-----------|---------------|
| leukocyte antigen p18-20/protectin/CD59                                                     | 107271                                   | M95708    | 11p13         |
| T-cell antigen CD46/membrane cofactor protein/MCP/measles virus receptor/CD46               | 120920                                   | Y07713    | 1q32          |
| erythrocyte antigen CD55/decay-accelerating factor for complement/DAF/CD55                  | 125240                                   | S72858    | 1q32          |
| leukocyte antigen p18-20/protectin/CD59                                                     | 107271                                   | M95708    | 11p13         |
| erythrocyte antigen CD35/complement receptor CR1 (receptor for components C3b/C4b)/CD35/CR1 | 120620                                   | AH002679  | 1q32          |
| complement component 3a receptor 1/C3AR1                                                    | *****                                    | NM_004054 | *****         |
| complement component 4-binding protein, alpha/C4BPA                                         | 120830                                   | NM_000715 | 1q32          |
| complement component 4-binding protein, beta/C4BPB                                          | 120831                                   | NM_000716 | 1q32          |
| complement component 5 receptor 1 (C5a ligand)/C5AR1                                        | 113995                                   | NM_001736 | Chr.19        |
| antigen CD21/CD21                                                                           | *****                                    | X98257    | *****         |
| Alternative Pathway                                                                         | B-factor, properdin/BF                   | NM_001710 | 6p21.3        |
|                                                                                             | properdin P factor, complement/PFC       | NM_002621 | Xp11.4-p11.23 |
|                                                                                             | adipsin/complement factor D precursor/DF | NM_001928 | *****         |

|                                           |                                                                          |        |           |              |
|-------------------------------------------|--------------------------------------------------------------------------|--------|-----------|--------------|
| Defensins and Related Protective Proteins | defensin, alpha 1, myeloid-related sequence/DEFA1                        | 125220 | NM_004084 | 8p23.2-p23.1 |
|                                           | defensin, alpha 3, neutrophil-specific/DEFA3                             | *****  | NM_005217 | *****        |
|                                           | defensin, alpha 4/corticostatin/DEFA4                                    | 601157 | NM_001925 | Chr.8        |
|                                           | defensin, alpha 5/DEFA5                                                  | 600472 | M97925    | 8pter-p21    |
|                                           | defensin, alpha 6, Paneth cell-specific/DEFA6                            | 600471 | NM_001926 | 8pter-p21    |
|                                           | defensin, beta 1/DEFB1                                                   | 602056 | NM_005218 | 8p23.2-p23.1 |
|                                           | defensin, beta 2/DEFB2                                                   | 602215 | NM_004942 | 8p23.1-p22   |
|                                           | ribonuclease, RNase A family, 2/eosinophil-derived neurotoxin/EDN/RNASE2 | 131410 | NM_002934 | 14q24-q31    |
|                                           | ribonuclease, RNase A family, 3/eosinophil cationic protein/ECP/RNASE3   | 31398  | NM_002935 | 14q24-q31    |
|                                           | myeloperoxidase/MPO                                                      | 254600 | J02694    | 17q23.1      |
|                                           | eosinophil peroxidase/EPX                                                | 131399 | NM_000502 | *****        |
|                                           | cathelicidin antimicrobial peptide/CAMP                                  | 600474 | NM_004345 | 3p21.3       |
|                                           | lysozyme/LYZ                                                             | 153450 | NM_000239 | Chr.12       |
|                                           | chitinase 1/CHIT1                                                        | 600031 | NM_003465 | 1q31-q32     |
|                                           | lactotransferrin/LTF                                                     | 150210 | NM_002343 | 3q21-q23     |
| Acute Protection                          |                                                                          |        |           |              |

# Pathogens

|                                                                                                        |        |           |               |
|--------------------------------------------------------------------------------------------------------|--------|-----------|---------------|
| polyadenylate binding protein/TIA1                                                                     | 603518 | M77142    | 2p13          |
| TIA1 cytotoxic granule-associated RNA-binding protein-like 1/TIAL1                                     | 603413 | NM_003252 | 10q           |
| granulysin/NKG5                                                                                        | 603082 | NM_006433 | 2p12-q11      |
| neutrophil azurocidin/NAZC                                                                             | 162815 | M96326    | 19p13.3       |
| bactericidal/permeability-increasing protein precursor/BPI                                             | 109195 | NM_001725 | 20q11.23-q12  |
| lipopolysaccharide-binding protein/LBP                                                                 | 151990 | AF105067  | 20q11.23-q12  |
| monocyte antigen CD14/monocyte differentiation antigen/CD14                                            | 158120 | NM_000591 | 5q31.1        |
| proteoglycan 1, secretory granule/serglycin/PRG1                                                       | 177040 | NM_002727 | 10q22.1       |
| proteoglycan 2, bone marrow/natural killer cell activator, eosinophil granule major basic protein/PRG2 | *****  | NM_002728 | *****         |
| prepro-major basic protein homolog/MBPH                                                                | *****  | NM_006093 | *****         |
| neuronal pentraxin I/NPTX1                                                                             | 602367 | NM_002522 | 17q25.1-q25.2 |
| neuronal pentraxin II/NPTX2                                                                            | 600750 | U26662    | 7q21.3-q22.1  |
| pentraxin-related gene, rapidly induced by IL-1 beta/PTX3                                              | 602492 | NM_002852 | 3q25          |
| amyloid P component, serum/APCS                                                                        | 104770 | NM_001639 | 1q21-q23      |
| C-reactive protein, pentraxin-related/CRP                                                              | 123260 | X56214    | 1q21-q23      |

## Pentraxins

|                                                                      |                  |                                                                                                |        |           |               |
|----------------------------------------------------------------------|------------------|------------------------------------------------------------------------------------------------|--------|-----------|---------------|
| Degranulation of Platelets, Mast Cells, Neutrophils, and Eosinophils | <b>Receptors</b> | mast cell IgE receptor alpha polypeptide/FCER1A                                                | 147140 | *****     | 1q23          |
|                                                                      |                  | mast cell IgE receptor beta polypeptide/FCER1B                                                 | 147138 | NM_000139 | 11q13         |
|                                                                      |                  | mast cell IgE receptor beta polypeptide/FCER1G                                                 | 147139 | NM_004106 | 1q23          |
|                                                                      |                  | granulocyte antigen CD62/platelet alpha-granule membrane protein/selectin P/CD62/SELP          | 173610 | NM_003005 | 1q23-q25      |
|                                                                      |                  | neutrophil antigen CD16/low-affinity receptor IIIA for Fc fragment of IgG/FCGR3A/CD16          | 146740 | M24853    | 1q23          |
|                                                                      |                  | prostaglandin I2 receptor/PTGIR/prostacyclin receptor                                          | 600022 | SEG_HUMI  | 19q13.3       |
|                                                                      |                  | formyl peptide receptor 1/FPRL1                                                                | 136537 | NM_002029 | Chr.19        |
|                                                                      |                  | formyl peptide receptor-like 1/FPRL1                                                           | 136538 | NM_001462 | 19q13.3-q13.4 |
|                                                                      |                  | formyl peptide receptor-like 2/FPRL2                                                           | 136539 | NM_002030 | 19q13.3-q13.4 |
|                                                                      |                  | lipoxin A4 receptor                                                                            | *****  | AF054013  | *****         |
|                                                                      | <b>Signaling</b> | inositol polyphosphate-5-phosphatase, 145 kD/SH2-containing inositol 5-phosphatase/SHIP/INPP5D | 601582 | NM_005541 | 2q36-q37      |
|                                                                      |                  | v-src-1 Yamaguchi sarcoma viral related oncogene homolog/LYN                                   | 165120 | NM_002350 | 8q13-qter     |
|                                                                      |                  | guanine nucleotide binding protein (G protein), q polypeptide/GNAQ                             | 600998 | NM_002072 | 9q21          |

|                                                                                                 |                |                                                                                                |        |           |               |
|-------------------------------------------------------------------------------------------------|----------------|------------------------------------------------------------------------------------------------|--------|-----------|---------------|
|                                                                                                 |                | guanine nucleotide binding protein (G protein), alpha inhibiting activity, polypeptide 2/GNAI2 | 139360 | NM_002070 | 3p21          |
| Release of Membrane Lipids<br>(common to PAF, lipoxin, leukotriene, and prostaglandin pathways) | Phospholipases | phospholipase A2 group                                                                         | 172411 | NM_000300 | 1p35          |
|                                                                                                 |                | phospholipase A2 group IB/PLA2G1B                                                              | 172410 | NM_000928 | 12q23-q24.1   |
|                                                                                                 |                | phospholipase A2 group X/PLA2G10                                                               | 603603 | NM_003561 | 16p13.1-p12   |
|                                                                                                 |                | phospholipase A2 group IVA/PLA2G4A                                                             | 600522 | U08374    | 1q25          |
|                                                                                                 |                | phospholipase A2 group VI/PLA2G6                                                               | 603604 | AF064594  | 22q13.1       |
|                                                                                                 |                | phospholipase A2 group IVC/PLA2G4C                                                             | 603602 | NM_003706 | chr. 19       |
|                                                                                                 |                | phospholipase A2 group V/PLA2G5                                                                | 601192 | NM_000929 | 1p36-p34      |
|                                                                                                 |                | phospholipase C, beta 2/PLCB2                                                                  | 604114 | NM_004573 | 15q15         |
|                                                                                                 |                | phospholipase C, beta 3/PLCB3                                                                  | 600230 | U26425    | 11q13         |
|                                                                                                 |                | phospholipase C, beta 4/PLCB4                                                                  | 600810 | NM_000933 | 20p12         |
|                                                                                                 |                | phospholipase C, delta 1/PLCD1                                                                 | 602142 | NM_006225 | 3p22-p21.3    |
|                                                                                                 |                | phospholipase C, epsilon/PLCE                                                                  | 600597 | NM_006226 | 2q33          |
|                                                                                                 |                | phospholipase C, gamma 1 (formerly subtype 148)/PLCG1                                          | 172420 | NM_002660 | 20q12-q13.1   |
|                                                                                                 |                | phospholipase C, gamma 2 (phosphatidylinositol-specific)/PLCG2                                 | 600220 | NM_002661 | 16q24.1       |
|                                                                                                 |                | lysosomal acid lipase/LIPB                                                                     | 278000 | NM_000235 | 10q24-q25     |
|                                                                                                 | Annexins       | lipocortin 1/annexin 1/ANXA1                                                                   | 151690 | V00546    | 9q11-q22      |
|                                                                                                 |                | lipocortin 2/annexin 2/ANXA2                                                                   | 151740 | D00017    | 15q21-q22     |
|                                                                                                 |                | lipocortin 3/annexin 3/ANXA3                                                                   | 106490 | M20560    | 4q21          |
|                                                                                                 |                | lipocortin 5/annexin 5/ANXA4                                                                   | 131230 | NM_001154 | 4q26-q28      |
|                                                                                                 |                | lipocortin 7/annexin 7/ANXA1                                                                   | 186360 | NM_004034 | 10q21.1-q21.2 |

|                                |                                                       |        |           |              |
|--------------------------------|-------------------------------------------------------|--------|-----------|--------------|
| <b>Arachidonate Metabolism</b> | arachidonate 12-lipoxygenase, 12R type/ALOX12B        | 603741 | NM_001139 | 17pter-p13.1 |
|                                | arachidonate 15-lipoxygenase/ALOX15                   | 152392 | NM_001140 | 17p13.3      |
|                                | arachidonate 15-lipoxygenase, second type/ALOX15B     | 603697 | NM_001141 | *****        |
|                                | prostaglandin endoperoxide synthetase 1/COX1/PTGS1    | 176805 | AH001520  | 9q32-q33.3   |
| <b>Biosynthesis</b>            | prostaglandin endoperoxide synthetase 2/COX2/PTGS2    | 600262 | NM_000963 | 1q25.2-q25.3 |
|                                | thromboxane A synthase 1/TBXAS1                       | 274180 | EG_D34613 | 7q34         |
|                                | prostaglandin D2 synthase (hematopoietic)             | 602598 | *****     | *****        |
|                                | prostaglandin D2 synthase (21kD, brain)/PTGDS         | 176803 | M61900    | *****        |
|                                | prostaglandin I2 synthase/prostacyclin synthase/PTGIS | 601699 | EG_D83393 | 20q13        |
|                                | prostaglandin E receptor 1, EP1 subtype/PTGER1        | 176802 | NM_000955 | 19p13.1      |
| <b>Prostaglandins</b>          | prostaglandin E receptor 2, EP2 subtype/PTGER2        | 176804 | *****     | 5p13.1       |
|                                | prostaglandin E receptor 3, EP3 subtype/PTGER3        | 176806 | NM_000957 | 1p31.2       |
|                                | prostaglandin E receptor 4, EP4 subtype/PTGER4        | 601586 | NM_000958 | 5p13.1       |
|                                | prostaglandin F receptor/PTGFR                        | 600563 | L24470    | 1p31.1       |
|                                | prostaglandin F2 receptor negative regulator/PTGFRN   | 601204 | U26664    | 1p13.1-q21.3 |
|                                |                                                       |        |           |              |
|                                |                                                       |        |           |              |
| <b>Receptors</b>               |                                                       |        |           |              |
|                                |                                                       |        |           |              |
|                                |                                                       |        |           |              |
|                                |                                                       |        |           |              |

|              |  |                                                                        |        |           |              |
|--------------|--|------------------------------------------------------------------------|--------|-----------|--------------|
|              |  | prostaglandin I2 receptor/PTGIR/prostacyclin receptor                  | 600022 | SEG_HUMI  | 19q13.3      |
|              |  | solute carrier family 21 (prostaglandin transporter), member 2/SLC21A2 | 601460 | NM_005630 | 3q21         |
| Catabolism   |  | 15-hydroxyprostaglandin dehydrogenase/HPGD                             | 601688 | NM_000860 | 4q34-q35     |
|              |  | aldo-keto reductase family 1, member C2/AKR1C2                         | 600450 | NM_001353 | 10p15-p14    |
|              |  | CDP-choline:alkylacetyl glycerol cholinephosphotransferase             | *****  | *****     | *****        |
| Receptors    |  | platelet activating factor receptor/PTAFR                              | 173393 | M88177    | 1p35-p34.3   |
|              |  | platelet activating factor acetylhydrolase 1/PAFAH1                    | 601690 | NM_005084 | 6p21.2-p12   |
| Catabolism   |  | platelet activating factor acetylhydrolase, isoform 1B, alpha          | 601545 | NM_000430 | 17p13.3      |
|              |  | platelet activating factor acetylhydrolase, isoform 1B, beta           | 602508 | NM_002572 | 11q23        |
|              |  | platelet activating factor acetylhydrolase, isoform 1B, gamma          | 603074 | NM_002573 | 19q13.1      |
|              |  | platelet activating factor acetylhydrolase 2/PAFAH2                    | 602344 | NM_000437 | *****        |
|              |  | arachidonate 5-lipoxygenase/ALOX5                                      | 152390 | NM_000698 | Chr.10       |
| Biosynthesis |  | arachidonate 5-lipoxygenase-activating protein/FLAP/ALOX5AP            | 603700 | NM_001629 | 13q12        |
|              |  | arachidonate 12-lipoxygenase, 12R type/ALOX12B                         | 603741 | NM_001139 | 17pter-p13.1 |



|                     |                                                              |                                                                 |               |                   |
|---------------------|--------------------------------------------------------------|-----------------------------------------------------------------|---------------|-------------------|
| <b>Lipoxins</b>     | Gamma-glutamyltranspeptidase<br>1/GGT1                       | 231950                                                          | J04131        | 22q11.1-<br>q11.2 |
|                     | Gamma-glutamyltranspeptidase<br>2/GGT2                       | 137181                                                          | AH002728      | 22q11.1           |
|                     | Gamma-glutamyltransferase-like<br>activity 1/GGTLA1          | 137168                                                          | NM_00412<br>1 | *****             |
|                     | lipoxin A4 receptor                                          | *****                                                           | AF054013      | *****             |
| <b>Leukotrienes</b> | <b>Catabolism</b>                                            |                                                                 |               |                   |
|                     | renal microsomal dipeptidase/DPEP1                           | 179780                                                          | NM_00441<br>3 | 16q24.3           |
|                     | <b>Synthesis</b>                                             | arachidonate 5-lipoxygenase/ALOX5                               | NM_00069<br>8 | Chr.10            |
|                     |                                                              | arachidonate 5-lipoxygenase-<br>activating protein/FLAP/ALOX5AP | NM_00162<br>9 | 13q12             |
|                     |                                                              | leukotriene A4 hydrolase/LTA4H<br>(aminopeptidase)              | NM_00089<br>5 | 12q22             |
|                     |                                                              | leukotriene C4 synthase/LTC4S                                   | NM_00089<br>7 | 5q35              |
|                     |                                                              | Gamma-glutamyltranspeptidase<br>1/GGT1                          | J04131        | 22q11.1-<br>q11.2 |
|                     |                                                              | Gamma-glutamyltranspeptidase<br>2/GGT2                          | AH002728      | 22q11.1           |
|                     |                                                              | Gamma-glutamyltransferase-like<br>activity 1/GGTLA1             | NM_00412<br>1 | *****             |
|                     | <b>Receptors</b>                                             |                                                                 |               |                   |
|                     | cysteinyl leukotriene receptor<br>1/CYSLT1                   | 300201                                                          | NM_00663<br>9 | Xq13-q21          |
|                     | leukotriene b4 receptor (chemokine<br>receptor-like 1)/LTB4R | 601531                                                          | NM_00075<br>2 | 14q11.2-<br>q12   |
|                     | <b>Catabolism</b>                                            |                                                                 |               |                   |
|                     | renal microsomal dipeptidase/DPEP1                           | 179780                                                          | NM_00441<br>3 | 16q24.3           |
| <b>Biosynthesis</b> | Histidine Decarboxylase                                      | 142704                                                          | M60445        | 15q21-q22         |

|                  |                   |                                                       |        |           |              |
|------------------|-------------------|-------------------------------------------------------|--------|-----------|--------------|
| <b>Histamine</b> | <b>Receptors</b>  | histamine H1 receptor/HRH1                            | 600167 | NM_000861 | 3p21-p14     |
|                  |                   | histamine H2 receptor/HRH2                            | 142703 | AB023486  | *****        |
|                  |                   | histamine H3 receptor/HRH3                            | *****  | NM_007232 | *****        |
|                  | <b>Catabolism</b> | Histamine N-methyltransferase                         | *****  | D16224    | chr. 2       |
|                  |                   | Amine oxidase (copper-containing)<br>2/AOC2           | 602268 | D88213    | 17q21        |
|                  |                   | Amine oxidase (copper-containing)<br>3/AOC3           | 603735 | AF054985  | 17q21        |
|                  | <b>Synthesis</b>  | aromatic L-Amino Acid                                 |        |           |              |
|                  |                   | Decarboxylase/AADC                                    | 107930 | M76180    | 7p11         |
|                  |                   | tryptophan hydroxylase/TPH                            | 191060 | X52836    | 11p15.3-p14  |
|                  |                   | 14-3-3 protein ETA                                    | 113508 | X78138    | 22q12        |
|                  |                   | 14-3-3 protein ZETA                                   | 601288 | M86400    | 2p25.2-p25.1 |
|                  |                   | 14-3-3 protein BETA                                   | 601289 | X57346    | 20q13.1      |
| <b>Serotonin</b> | <b>Receptors</b>  | 14-3-3 protein SIGMA                                  | 601290 | X57348    | *****        |
|                  |                   | serotonin 5-HT receptors 5-HT1A, G<br>protein-coupled | 109760 | X57829    | 5q11.2-q13   |
|                  |                   | serotonin 5-HT receptors 5-HT1B, G<br>protein-coupled | 182131 | M81590    | 6q13         |
|                  |                   | serotonin 5-HT receptors 5-HT1C, G<br>protein-coupled | 312861 | U49516    | Xq24         |
|                  |                   | serotonin 5-HT receptors 5-HT1D, G<br>protein-coupled | 182133 | M81590    | 1p36.3-p34.3 |
|                  |                   | serotonin 5-HT receptors 5-HT1E, G<br>protein-coupled | 182132 | M91467    | 6q14-q15     |
|                  |                   | serotonin 5-HT receptors 5-HT1F, G<br>protein-coupled | 182134 | L05597    | 3p12         |
|                  |                   |                                                       |        |           |              |
|                  |                   |                                                       |        |           |              |
|                  |                   |                                                       |        |           |              |
|                  |                   |                                                       |        |           |              |
|                  |                   |                                                       |        |           |              |

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|----------------------|------------|----------------------------------------------------|--------|-----------|----------------|
|                      |            | serotonin 5-HT receptors 5-HT2A, G protein-coupled | 182135 | D87030    | 13q14-q21      |
|                      |            | serotonin 5-HT receptors 5-HT2B, G protein-coupled | 601122 | X77307    | 2q36.3-q37.1   |
|                      |            | serotonin 5-HT receptors 5-HT2C, G protein-coupled | 312861 | U49516    | Xq24           |
|                      |            | serotonin transporter                              | 182138 | X70697    | 17q11.1-q12    |
|                      | Catabolism | monoamine oxidase A/MAOA                           | 309850 | M69226    | Xp11.23        |
|                      |            | monoamine oxidase B/MAOB                           | 309860 | M69177    | Xp11.23        |
|                      |            | serotonin N-Acetyltransferase/SNAT                 | 600950 | U40347    | 17q25          |
|                      |            | tryptophan 2,3-dioxygenase/TDO2                    | 191070 | NM_005651 | 4q31-q32       |
| Nitric Oxide Pathway | Synthesis  | nitric oxide synthetase 1/NOS1                     | 163731 | AH001515  | 12q24.2-q24.31 |
|                      |            | nitric oxide synthetase 2A/NOS2A                   | 163730 | X85766    | 17cen-q11.2    |
|                      |            | macrophage nitric oxide synthetase 2B/NOS2B        | 600719 | AH006623  | 17p13.1-q25    |
|                      |            | macrophage nitric oxide synthetase 2C/NOS2C        | 600720 | 600720    | 17p13.1-q25    |
|                      |            | nitric oxide synthetase 3/NOS3                     | 163729 | AH001515  | 7q36           |
|                      |            | chondrocyte nitric oxide synthetase 3/NOS4         | 163728 | X73029    | *****          |
|                      |            | arginase/ARG1                                      | 207800 | NM_000045 | *****          |
|                      |            | arginase/ARG2                                      | 107830 | NM_001172 | 14q24.1-q24.3  |
|                      |            | endothelin 1/EDN1                                  | 131240 | NM_001955 | 6p24-p23       |
|                      |            | endothelin 2/EDN2                                  | 131241 | NM_001956 | 1p34           |
|                      | Synthesis  | endothelin 3/EDN3                                  | 131242 | NM_000114 | 10q13.2-q13.3  |

|                                           |                   |                  |                                                     |        |           |            |
|-------------------------------------------|-------------------|------------------|-----------------------------------------------------|--------|-----------|------------|
| <b>Vascularization</b>                    | <b>Endothelin</b> |                  | endothelin converting enzyme 1/ECE1                 | 600423 | NM_001397 | 1p36.1     |
|                                           | <b>Receptor</b>   |                  | endothelin A receptor isoform delta 3/EDNRA         | 131243 | AF014826  | Chr.4      |
| <b>Vascular Endothelial Growth Factor</b> |                   |                  | endothelin receptor type B/EDNRB                    | 131244 | NM_000115 | 13q22      |
|                                           |                   | <b>Synthesis</b> | vascular endothelial growth factor A/VEGFA          | 192240 | M32977    | 6p12       |
|                                           |                   |                  | vascular endothelial growth factor B/VEGFB          | 601398 | U52819    | 11q13      |
|                                           |                   |                  | vascular endothelial growth factor C/VEGFC          | 601528 | X94216    | *****      |
|                                           |                   | <b>Receptor</b>  | VEGF receptor                                       | 191306 | X61656    | 4q12       |
|                                           |                   | <b>Synthesis</b> | dopamine beta hydroxylase/DBH                       | 223360 | Y00096    | 9q34       |
|                                           |                   |                  | phenylethanolamine-N-methyltransferase/PNMT         | 171190 | NM_002686 | 17q21-q22  |
|                                           |                   |                  | tyrosine hydroxylase/TH                             | 191290 | X05290    | 11p15.5    |
|                                           |                   |                  | alpha-1A-adrenergic                                 | 104219 | M76446    | Chr.20     |
|                                           |                   |                  | alpha-1B-adrenergic                                 | 104220 | L31773    | 5q33       |
| <b>Receptors</b>                          |                   |                  | alpha-1C-adrenergic                                 | 104221 | D25235    | 8p21       |
|                                           |                   |                  | alpha-1D-adrenergic                                 | 104222 | M76446    | 20p13      |
|                                           |                   |                  | alpha-2A-adrenergic                                 | 104210 | M18415    | 10q24-q26  |
|                                           |                   |                  | alpha-2B-adrenergic                                 | 104260 | AF005900  | Chr.2      |
|                                           |                   |                  | alpha-2C-adrenergic                                 | 104250 | J03853    | 4q16.1     |
|                                           |                   |                  | alpha-2D-adrenergic                                 | 109630 | J03019    | 10q24-q26  |
|                                           |                   |                  | beta-1-adrenergic receptor/ADRB1                    | 109690 | M15169    | 5q32-q34   |
|                                           |                   |                  | Beta-2-Adrenergic Receptor/ADRB2                    | 109635 | NM_001619 | 11cen-q13  |
|                                           |                   |                  | beta-adrenergic receptor kinase 1/BARK1             | 109760 | X57829    | 5q11.2-q13 |
|                                           |                   |                  | Beta-2-Adrenergic Receptor-Like Protein G-21/ADRB2L | 109691 | X70811    | 8p12-p11.2 |
|                                           |                   |                  | Beta-3-Adrenergic Receptor/ADRB3                    |        |           |            |

|                                               |                                                                   |        |               |           |
|-----------------------------------------------|-------------------------------------------------------------------|--------|---------------|-----------|
| <b>Epinephrine<br/>and<br/>Norepinephrine</b> | Beta-Adrenergic Receptor Kinase<br>1/ADRBK1                       | 109635 | X61157        | 11cen-q13 |
|                                               | Beta-Adrenergic Receptor Kinase<br>2/ADRBK2                       | 109636 | X69117        | 22q11     |
| <b>Response</b>                               | phosphodiesterase 4A, cAMP-<br>specific/PDE4A                     | 600126 | NM_00620<br>2 | 19p13.2   |
|                                               | phosphodiesterase 4B, cAMP-<br>specific/PDE4B                     | 600127 | NM_00260<br>0 | 1p31      |
|                                               | phosphodiesterase 4C, cAMP-<br>specific/PDE4C                     | 600128 | *****         | Chr.19    |
|                                               | phosphodiesterase 4D, cAMP-<br>specific/PDE4D                     | 600129 | NM_00620<br>3 | 5q12      |
|                                               | phosphodiesterase 7A, cAMP-<br>specific/PDE7A                     | 171885 | L12052        | 8q13-q22  |
|                                               | phosphodiesterase 8A, cAMP-<br>specific/PDE8A                     | 602972 | AF056490      | *****     |
|                                               | phosphodiesterase 9A, cAMP-<br>specific/PDE9A                     | 602973 | NM_00260<br>6 | 21q22.3   |
|                                               | Vesicular Amine Transporter 2/VAT2                                | 193001 | L09118        | 10q25     |
|                                               | Vesicular Amine Transporter 1/VAT1                                | 193002 | *****         | 8p21.3    |
| <b>Uptake</b>                                 | Solute carrier family 6, member<br>5/SLC6A2/NAT1/NET1             | 163970 | NM_00104<br>3 | 16q12.2   |
|                                               | Monoamine Oxidase A/MAOA                                          | 309850 | M69226        | Xp11.23   |
|                                               | Monoamine Oxidase B/MAOB                                          | 309860 | M69177        | Xp11.23   |
| <b>Catabolism</b>                             | Catechol-O-Methyltransferase/COMT                                 | 116790 | M58525        | 22q11.2   |
|                                               | Aromatic L-Amino Acid<br>Decarboxylase/AADC/dopa<br>decarboxylase | 107930 | M76180        | 7p11      |
| <b>Biosynthesis</b>                           | Tyrosine Hydroxylase                                              | 191290 | X05290        | 11p15.5   |

|                 |                     |                                                   |        |           |               |
|-----------------|---------------------|---------------------------------------------------|--------|-----------|---------------|
| <b>Dopamine</b> | <b>Receptors</b>    | Dopamine Receptor D1                              | 126449 | X58987    | 5q35.1        |
|                 |                     | Dopamine Receptor D2/DRD2                         | 126450 | NM_000795 | 11q23         |
|                 |                     | Dopamine Receptor D3/DRD3                         | 126451 | U32499    | 3q13.3        |
|                 |                     | Dopamine Receptor D4                              | 126452 | L12398    | 11p15.5       |
|                 |                     | Dopamine Receptor D5                              | 126453 | M67439    | 4p16.1-p15.3  |
|                 | <b>Reuptake</b>     | Dopamine Transporter/ DAT1                        | 126455 | L24178    | 5p15.3        |
|                 | <b>Catabolism</b>   | Dopamine Beta-Hydroxylase/monooxygenase           | 223360 | Y00096    | 9q34          |
|                 |                     | Catechol-O-Methyltransferase                      | 116790 | M58525    | 22q11.2       |
|                 |                     | Monoamine Oxidases A                              | 309850 | M69226    | Xp11.23       |
|                 |                     | Monoamine Oxidases B                              | 309860 | M69177    | Xp11.23       |
|                 |                     | Phenol Sulfotransferase 1                         | 171150 | L10819    | 16p12.1-p11.2 |
|                 |                     | Phenol Sulfotransferase 2                         | 601292 | X78282    | 16p12.1-p11.2 |
|                 |                     | Phenol Sulfotransferase 3                         | 600641 | L19956    | 16p11.2       |
|                 | <b>Biosynthesis</b> | adenylosuccinate lyase/ADSL                       | 103050 | NM_000026 | 22q13.1       |
|                 |                     | adenylosuccinate synthetase/ADSS                  | 103060 | NM_001126 | 1cen-q12      |
|                 |                     | Adenosine A1 Receptor; Adora1/G protein-coupled   | 102775 | L22214    | 1q32.1        |
|                 |                     | Adenosine A2 Receptor; Adora2a/G protein-coupled  | 102776 | X68486    | 22q11.2       |
|                 |                     | Adenosine A2b Receptor; Adora2b/G protein-coupled | 600446 | X68487    | 17p12-p11.2   |
|                 |                     | Adenosine A3 Receptor; Adora3/G protein-coupled   | 600445 | L20463    | 1p21-p13      |
|                 |                     |                                                   |        |           |               |

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|--------------|------------|---------------------------------------------------------------|--------|-----------|---------------|
| Adenosine    | Receptors  | Adenosine A2 Receptor-like/ADORA2L1                           | 102777 | *****     | 10q25.3-q26.1 |
|              |            | Purinergic Receptor P2x, Ligand-Gated Ion Channel, 1; P2rx1   | 600845 | NM_002558 | *****         |
|              |            | Purinergic Receptor P2x, Ligand-Gated Ion Channel, 3; P2rx3   | 600843 | Y07683    | 11q12         |
|              |            | Purinergic Receptor P2x, Ligand-Gated Ion Channel, 4; P2rx4   | 600846 | AF000234  | 12q24.32      |
|              |            | Purinergic Receptor P2x, Ligand-Gated Ion Channel, 5; P2rx5   | 602836 | NM_002561 | *****         |
|              |            | Purinergic Receptor P2x, Ligand-Gated Ion Channel, 7; P2rx7   | 602566 | Y09561    | 12q24         |
|              |            | P2Y11 purinoceptor/G protein-receptor                         | 602697 | *****     | *****         |
|              |            | P2Y7 purinoceptor/leukotriene B4 receptor/G protein-coupled   | 601531 | NM_000752 | 14q11.2-q12   |
|              |            | P2Y2 purinoceptor/G protein-coupled                           | 600041 | U07225    | 1q13.5-q14.1  |
|              |            | P2Y1 purinoceptor/G protein-coupled                           | 601167 | U42029    | 3q25          |
|              |            | P2Y4 pyrimidinergic receptor/G protein-coupled                | 300038 | NM_002565 | Xq13          |
|              |            | P2Y6 pyrimidinergic receptor/G protein-coupled                | 602451 | NM_004154 | 11q13.5       |
|              | Reuptake   | Solute carrier family 29 (nucleosides), member 1/SLC29A1/ENT1 | 602193 | NM_004955 | 6p21.2-p21.1  |
|              |            | Solute carrier family 29 (nucleosides), member 2/SLC29A2/ENT2 | 602110 | X86681    | 11q13         |
|              | Catabolism | adenosine deaminase                                           | 102700 | NM_000022 | 20q13.11      |
| Biosynthesis |            | Choline acetyltransferase/CHAT                                | 118490 | NM_003055 | 10q11.2       |
|              |            | carnitine acetyltransferase/CRAT                              | 600184 | NM_004003 | 9q34.1        |
|              |            | apolipoprotein E                                              | 107741 | NM_000041 | 19q13.2       |

| Neurotransmitter and Peptide Hormone Inflammatory Modulation | Acetylcholine | Receptors                                            |        |           |               |  |
|--------------------------------------------------------------|---------------|------------------------------------------------------|--------|-----------|---------------|--|
|                                                              |               | Cholinergic Receptor, Muscarinic, 1;<br>CHRM1        | 118510 | X15263    | 11q13         |  |
|                                                              |               | Cholinergic Receptor, Muscarinic, 2;<br>CHRM2        | 118493 | U19800    | 7q35-q36      |  |
|                                                              |               | Cholinergic Receptor, Muscarinic, 3;<br>CHRM3        | 118494 | U29589    | 1q41-q44      |  |
|                                                              |               | Cholinergic Receptor, Muscarinic, 4;<br>CHRM4        | 118495 | M16405    | 11p12-p11.2   |  |
|                                                              |               | Cholinergic Receptor, Muscarinic, 5;<br>CHRM5        | 118496 | AF026263  | 15q26         |  |
|                                                              |               | Nicotinic, Cholinergic receptor alpha 1              | 100690 | X70108    | 2q24-q32      |  |
|                                                              |               | Nicotinic, Cholinergic receptor alpha 2              | 118502 | U62431    | Chr.8         |  |
|                                                              |               | Nicotinic, Cholinergic receptor alpha 3              | 118503 | X53559    | 15q24         |  |
|                                                              |               | Nicotinic, Cholinergic receptor alpha 4              | 118504 | U62433    | 20q13.2-q13.3 |  |
|                                                              |               | Nicotinic, Cholinergic receptor alpha 5              | 118505 | M83712    | 15q24         |  |
|                                                              |               | Nicotinic, Cholinergic receptor alpha 7/CHRNA7       | 118511 | U40583    | 15q14         |  |
|                                                              |               | Nicotinic, Cholinergic receptor beta 1               | 100710 | X14830    | 17p12-p11     |  |
|                                                              |               | Nicotinic, Cholinergic receptor beta 2               | 118507 | Y08415    | 1p21          |  |
|                                                              |               | Nicotinic, Cholinergic receptor beta 3               | 118508 | X67513    | 8p11.2        |  |
|                                                              |               | Nicotinic, Cholinergic receptor beta 4               | 118509 | X68275    | 15q24         |  |
|                                                              |               | Nicotinic, Cholinergic receptor epsilon polypeptide  | 100725 | X66403    | Chr.17        |  |
|                                                              |               | Nicotinic, Cholinergic receptor,                     | 100720 | X55019    | 2q33-q34      |  |
|                                                              |               | Nicotinic, Cholinergic receptor,                     | 100730 | NM_005199 | 2q33-q34      |  |
|                                                              |               | Vesicular acetylcholine transporter                  | 600336 | NM_003055 | 10q11.2       |  |
|                                                              |               | Reuptake                                             |        |           |               |  |
|                                                              |               | Acetylcholinesterase/ACHE                            | 100740 | M55040    | 7q22          |  |
|                                                              | Catabolism    | butyrylcholinesterase 1/serum cholinesterase 1/BCHE1 | 177400 | NM_000053 | 26.1-q26.2    |  |



|  |                                                                      |        |           |           |
|--|----------------------------------------------------------------------|--------|-----------|-----------|
|  | butyrylcholinesterase 2/serum cholinesterase 2/BCHE2                 | 177500 | *****     | 2q33-q35  |
|  | voltage-dependent calcium channel, P/Q type, alpha 1A                | 141500 | NM_000068 | 19p13     |
|  | calcium channel, voltage-dependent, L type, alpha 1B subunit/CACNA1B | 601012 | NM_000718 | 9q34      |
|  | calcium channel, voltage-dependent, L type, alpha 1C subunit/CACNA1C | 114205 | NM_000719 | 12p13.3   |
|  | calcium channel, voltage-dependent, L type, alpha 1D subunit/CACNA1D | 114206 | NM_000720 | 3p14.3    |
|  | L-type voltage dependent calcium channel alpha 1S subunit/CACNA1S    | 114208 | NM_000069 | 1q32      |
|  | calcium channel, voltage-dependent, beta 1 subunit/CACNB1            | 114207 | NM_000723 | 17q21-q22 |
|  | voltage dependent calcium channel beta 2 subunit/CACNB2              | 600003 | U07139    | 10p12     |
|  | calcium channel, voltage-dependent, alpha 2/delta subunit/CACNA2D1   | 114204 | Z28613    | 7q21-q22  |
|  | calcium channel, voltage-dependent, gamma subunit/CACNG              | 114209 | NM_000727 | 17q24     |
|  | neuronal voltage dependent calcium channel gamma subunit/CACNG2      | 602911 | NM_006078 | *****     |
|  | sodium channel, nonvoltage-gated 1, beta (Liddle syndrome)/SCNN1B    | 600760 | NM_000336 | 16p13-p12 |
|  | sodium channel, nonvoltage-gated 1, gamma/SCNN1G                     | 600761 | NM_001039 | 16p13-p12 |
|  | cyclic nucleotide gated hyperpolarization activated potassium        | 602780 | AF064876  | *****     |

|                           |                                                                                         |        |           |          |
|---------------------------|-----------------------------------------------------------------------------------------|--------|-----------|----------|
| <b>Potassium Channels</b> | cyclic nucleotide gated hyperpolarization activated potassium                           | 602781 | AF064877  | *****    |
|                           | potassium inwardly-rectifying channel, subfamily J, member 2 (KCNJ2)                    | 600681 | NM_000891 | Chr. 17  |
|                           | voltage dependent potassium channel, subfamily K, member 2/KCNK2                        | 603219 | *****     | 1q41     |
|                           | G protein coupled potassium channel, subfamily J, member                                | 601534 | NM_002239 | 2q24.1   |
|                           | G protein coupled potassium channel inward rectifier/GIRK3                              | 600932 | *****     | 1q21-q23 |
|                           | voltage dependent potassium channel, subfamily S, member 3/KCNK3                        | 603888 | AF043472  | 2p24     |
|                           | potassium voltage-gated channel precursor, KQT-like subfamily, member 1/KCNQ1           | 192500 | NM_000218 | 11p15.5  |
|                           | potassium intermediate/small conductance calcium-activated channel, subfamily N, member | 602754 | NM_002250 | 19q13.2  |
|                           | chloride channel, calcium activated, family member 1/CLCA1                              | 603906 | NM_001285 | 1p31-p22 |
|                           | chloride channel, calcium activated, family member 2/CLCA2                              | 604003 | NM_006536 | *****    |
| <b>Chloride</b>           | cystic fibrosis transmembrane conductance regulator/CFTR                                | 602421 | NM_000492 | 7q31.2   |
|                           | membrane metalloendopeptidase/MME/neutral endopeptidase                                 | 120520 | AH002677  | 3q21-q27 |
|                           | proopiomelanocortin                                                                     | 176830 | NM_000939 | 2p23.3   |
|                           |                                                                                         |        |           |          |

|         |              |                                                    |        |           |               |
|---------|--------------|----------------------------------------------------|--------|-----------|---------------|
| Opioids | Biosynthesis | prepronociceptin/nociceptin/nosistatin/<br>PNOC    | 601459 | *****     | 8p21          |
|         |              | preproenkephalin                                   |        |           |               |
|         |              | B/prodynorphin/PDYN                                | 131340 | NM_006211 | 20pter-p12.21 |
|         |              | preproenkephalin                                   |        |           |               |
|         |              | A/proenkephalin/PENK                               | 131330 | NM_006211 | 8q23-q24      |
|         | Receptors    | Opioid Receptor, Mu-1; Oprm1                       | 600018 | NM_000914 | 6q24-q25      |
|         |              | Opioid Receptor, Kappa-1; Oprk1                    | 165196 | U17298    | 8q11.2        |
|         |              | opioid receptor-like 1/OPRL 1                      | 602548 | X77130    | *****         |
|         |              | Opioid Receptor, Delta-1; Oprd1                    | 165195 | U10504    | 1p36.1-p34.3  |
|         |              | Opioid Receptor, Sigma 1                           | 601978 | U75283    | *****         |
|         |              | opioid binding cell adhesion<br>molecule/OBCAM     | 600632 | *****     | Chr.11        |
|         |              | G protein-coupled receptor 7/GPR7                  | 600730 | U22491    | 0q11.2-q21.1  |
|         |              | G protein-coupled receptor 8/GPR8                  | 600731 | U22492    | 20q13.3       |
| Leptin  | Biosynthesis | leptin/LEP                                         | 164160 | NM_000230 | 7q31.3        |
|         | Receptor     | leptin receptor/LEPR                               | 601007 | NM_002303 | 1p31          |
|         | Biosynthesis | Cholecystokinin/CCK                                | 118440 | L00354    | 3pter-p21     |
|         | Receptors    | Cholecystokinin A receptor/CCKAR                   | 118444 | L13605    | 4p15.2-p15.1  |
|         |              | Cholecystokinin B receptor/CCKBR                   | 118445 | L08112    | 1p15.5-p15.4  |
|         |              | Neurokinin A/Tachykinin 1 or<br>2/Substance P or K | 162320 | U37529    | 7q21-q22      |
|         | Biosynthesis | Neurokinin B/Tachykinin 3                          | 162330 | *****     | 12q13-q21     |
|         | Receptors    | Tachykinin NK1 receptor/TACR1                      | 162323 | M81797    | Chr.2         |
|         |              | Tachykinin NK2 receptor/TACR2                      | 162321 | M57414    | 10q11-q21     |
|         |              | Tachykinin NK3 receptor/TACR3                      | 162332 | M89473    | *****         |
|         | Biosynthesis | kininogen/KNK                                      | 228960 | *****     | 3q27          |
|         |              | kallikrein 1/KLK1                                  | 147910 | AH002853  | 9q13.2-q13.4  |

|                                                                |                                           |                                                                              |        |              |               |
|----------------------------------------------------------------|-------------------------------------------|------------------------------------------------------------------------------|--------|--------------|---------------|
| Bradykinin                                                     | Receptor                                  | bradykinin receptor B1/BDKRB1 G protein-coupled                              | 600337 | NM_000710    | 4q32.1-q32.2  |
|                                                                |                                           | bradykinin receptor B2/BDKRB2 G protein-coupled                              | 113503 | NM_000623    | 4q32.1-q32.2  |
|                                                                | Biosynthesis                              | parathyroid hormone-related protein/parathyroid hormone-like hormone/PTH LH  | 168470 | NM_002820    | 12p12.1-p11.2 |
| Parathyroid Hormone (PTH)                                      |                                           | parathyroid hormone/PTH                                                      | 168450 | NM_000315    | 1p15.3-p15.1  |
|                                                                | Receptors                                 | parathyroid hormone receptor                                                 | 168468 | NM_000316    | 3p22-p21.1    |
|                                                                |                                           | parathyroid hormone receptor                                                 | 601469 | NM_005048    | 2q33          |
| ACTH                                                           | Biosynthesis                              | proopi melanocortin                                                          | 176830 | NM_000939    | 2p23.3        |
|                                                                |                                           | melanocortin 1 receptor (alpha melanocyte stimulating hormone receptor)/MC1R | 155555 | NM_002386    | 16q24.3       |
|                                                                |                                           | melanocortin 2 receptor/ACTH receptor/MC2R                                   | 202200 | NM_000529    | 18p11.2       |
|                                                                |                                           | melanocortin 4 receptor/MC4R                                                 | 155541 | NM_005912    | 18q22         |
|                                                                | Receptor                                  | melanocortin 5 receptor/MC5R                                                 | 600042 | NM_005913    | 18p11.2       |
|                                                                | Receptors                                 | Folate Receptor Alpha/FOLR1                                                  | 136430 | M28099       | 1q13.3-q13.5  |
|                                                                |                                           | Folate Receptor Beta/FOLR2                                                   | 136425 | AF000380     | 1q13.3-q13.5  |
|                                                                |                                           | Folate Receptor Gamma/FOLR3                                                  | 602469 | Z32564       | *****         |
|                                                                | Transporter                               | Folate Transporter (SLC19A1)                                                 | 600424 | U19720       | 21q22.3       |
|                                                                | Glutaminat ion                            | Vitamin B12 binding protein                                                  | 275350 | NM_000355    | 22q11.2-qter  |
| folypolyglutamate synthetase/FPGS gamma-glutamyl hydrolase/GGH |                                           | 136510                                                                       | M98045 | 9cen-q34     |               |
|                                                                |                                           | 601509                                                                       | U55206 | *****        |               |
|                                                                | Methylenetetrahydrofolate reductase/MTHFR | 236250                                                                       | U09806 | 1p36.3       |               |
|                                                                | Dihydrofolate reductase/DHFR              | 126060                                                                       | J00140 | 5q11.2-q13.2 |               |

**Folate  
Metabolism**

**Metabolism**

|                                                                                                                                          |        |           |              |
|------------------------------------------------------------------------------------------------------------------------------------------|--------|-----------|--------------|
| 5,10-methylenetetrahydrofolate dehydrogenase, 5,10-methylenetetrahydrofolate cyclohydrolase, 10-formyltetrahydrofolate synthetase/MTHFD1 | 172460 | NM_005956 | 14q24        |
| 5,10-methylenetetrahydrofolate synthetase (5-formyltetrahydrofolate cyclo-ligase)/MTHFS                                                  | 604197 | NM_006441 | Chr. 15      |
| phosphoribosylglycinamide formyltransferase, phosphoribosylglycinamide synthetase,                                                       |        |           |              |
| phosphoribosylaminoimidazole                                                                                                             | 138440 | NM_000819 | 21q22.1      |
| folate hydrolase 1/FOH1                                                                                                                  | 600934 | NP_004467 | 11q14        |
| 6-pyruvoyl tetrahydrobiopterin synthase/PTPS                                                                                             | 261640 | Q03393    | 1q22.3-q23.2 |
| serine hydroxymethyltransferase 1 (soluble)/SHMT1                                                                                        | 182144 | NM_004169 | 17p11.2      |
| serine hydroxymethyltransferase 2 (mitochondrial)/SHMT2                                                                                  | 138450 | NM_005412 | 12q13        |
| Glycine aminotransferase/glycine cleavage T protein/GAT                                                                                  | 238310 | NM_000481 | 3p21.2-p21.1 |
| 5-methyltetrahydrofolate-homocysteine methyltransferase/methionine                                                                       | 156570 | NM_000254 | 1q43         |
| glutamate                                                                                                                                |        |           |              |
| formiminotransferase/dihydrofolate synthetase                                                                                            | 229100 | *****     | *****        |

|                            |                          |                          |                                                    |        |           |            |
|----------------------------|--------------------------|--------------------------|----------------------------------------------------|--------|-----------|------------|
| <b>General Cell Growth</b> | <b>Purine Metabolism</b> | <b>Purine Metabolism</b> | hypoxanthine-guanine phosphoribosyltransferase     | 308000 | M31642    | Xq26-q27.2 |
|                            |                          |                          | adenosine phosphoribosyltransferase/APRT           | 102600 | NM_000485 | 16q24      |
|                            |                          |                          | thiopurine S-methyltransferase/TPMT                | 187680 | NM_000367 | 6p22.3     |
|                            |                          |                          | IMP (inosine monophosphate) dehydrogenase 1/IMPDH1 | 146690 | NM_000883 | 7q31.3-q32 |
|                            |                          |                          | IMP (inosine monophosphate) dehydrogenase 2/IMPDH2 | 146691 | NM_000884 | 3p21.2     |
|                            |                          |                          | adenylosuccinate synthetase/ADSS                   | 103060 | NM_001126 | 1cen-q12   |
|                            |                          |                          | adenylosuccinate lyase                             | 103050 | NM_000026 | 22q13.1    |
|                            |                          |                          | glycinamide ribotide formyltransferase             | 138440 | X54199    | 21q22.1    |
|                            |                          |                          | urate oxidase                                      | 191540 | AH003594  | 1p22       |
|                            |                          |                          | purine nucleoside phosphorylase                    | 164050 | NM_000270 | 14q13.1    |
|                            |                          |                          | xanthine oxidase                                   | 278300 | NM_000379 | 2p23-p22   |
|                            |                          |                          | adenosine deaminase                                | 102700 | NM_000022 | 20q13.11   |
|                            | <b>Cytoskeleton</b>      | <b>Tubulin</b>           | beta tubulin/TUBB                                  | 191130 | NM_001069 | 6p21.3     |
|                            |                          |                          | beta tubulin 2/TUBB2                               | 602660 | NM_006088 | *****      |
|                            |                          |                          | beta tubulin 4/TUBB4                               | 602661 | NM_006086 | *****      |
|                            |                          |                          | beta tubulin 5/TUBB5                               | 602662 | NM_006087 | *****      |

| Table 5. Meatbolism and Endocrinology Gene List |         |          |                                     |        |           |              |
|-------------------------------------------------|---------|----------|-------------------------------------|--------|-----------|--------------|
| Class                                           | Pathway | Function | Name                                | OMIM   | GID       | Locus        |
|                                                 |         |          | membrane                            |        |           |              |
|                                                 |         |          | metalloendopeptidase/neutral        | 120520 | NM_000902 | 3q21-q27     |
|                                                 |         |          | calpain, large polypeptide L3/CAPN3 | 114240 | NM_000070 | 5q15.1-q21.1 |
|                                                 |         |          | leucyl/cystinyl                     | 151300 | NM_005575 | *****        |
|                                                 |         |          | carboxypeptidase N polypeptide      |        |           |              |
|                                                 |         |          | 1/CPN1                              | 603103 | NM_001308 | chr. 10      |

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|                               |                                                                      |        |           |               |
|-------------------------------|----------------------------------------------------------------------|--------|-----------|---------------|
| Anterior pituitary<br>Hormone | Corticotropin releasing hormone receptor 2/CRHR2                     | 602034 | NM_001883 | 7p21-p15      |
|                               | Corticotropin releasing hormone-binding protein/CRHBP                | 122559 | NM_001882 | 5q11.2-q13.3  |
|                               | proopiomelanocortin/POMC                                             | 176830 | NM_000939 | 2p23.3        |
| ACTH                          | melanocortin 2 receptor/ACTH receptor/MC2R                           | 202200 | NM_000529 | 18p11.2       |
|                               | thyrotropin releasing hormone/TRH                                    | 275120 | NM_007117 | 3p            |
| TRH                           | thyrotropin releasing hormone receptor/G protein coupled/TRHR        | 188545 | NM_003301 | 8q23          |
|                               | cAMP responsive element binding protein 1/CREB1                      | 123810 | NM_004379 | 2q32.3-q34    |
| TSH                           | chorionic gonadotropin alpha chain/TSHA/CGA                          | 118850 | NM_000735 | 6q21.1-q23    |
|                               | thyroid stimulating hormone beta chain/TSHB                          | 188540 | NM_000549 | 1p13          |
|                               | thyroid stimulating hormone receptor/TSHR                            | 603372 | NM_000369 | 14q31         |
|                               | solute carrier family 5 (sodium iodide symporter), member 5/SLC5A5   | 601843 | NM_000453 | 19p13.2-p12   |
| Thyroid<br>Hormone            | thyroid peroxidase (nuclear gene encoding mitochondrial protein)/TPO | 274500 | NM_000547 | 2p25          |
|                               | thyroglobulin/TG                                                     | 188450 | NM_003235 | 8q24.2-q24.3  |
|                               | thyroxine-binding globulin/TBG                                       | 314200 | NM_000354 | Xq22.2        |
|                               | transthyretin (prealbumin, amyloidosis type I)/TTR                   | 176300 | NM_000371 | 18q11.2-q12.1 |

|                                                 |                                                               |                                                                                                               |        |               |                   |
|-------------------------------------------------|---------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------|--------|---------------|-------------------|
| Peptide<br>Hormones<br>Control of<br>Metabolism | Thyroid<br>Hormone<br>Synthesis                               | deiodinase, iodothyronine, type<br>I/DIO1                                                                     | 147892 | NM_00079<br>2 | 1p33-p32          |
|                                                 |                                                               | deiodinase, iodothyronine, type<br>II/DIO2                                                                    | 601413 | NM_00079<br>3 | 14q24.2-<br>q24.3 |
|                                                 |                                                               | thyroid hormone receptor, alpha (avian<br>erythroblastic leukemia viral (v-erb-a)<br>oncogene homolog)/THRA   | 190120 | NM_00325<br>0 | 17q11.2           |
|                                                 |                                                               | thyroid hormone receptor, alpha (avian<br>erythroblastic leukemia viral (v-erb-a)<br>oncogene homolog 2)/THRB | 190160 | S57224        | 3p24.3            |
|                                                 |                                                               | thyroid hormone receptor coactivating<br>protein/SMAP                                                         | 601836 | NM_00669<br>6 | *****             |
|                                                 |                                                               | silencing mediator for retinoid and<br>thyroid hormone receptors/SMRT                                         | 600848 | NM_006312     | *****             |
|                                                 |                                                               | retinoic and thyroid hormone receptor<br>associated corepressor<br>1/TRAC1/NCOR1                              | 600849 | NM_006311     | *****             |
|                                                 |                                                               | deiodinase, iodothyronine, type<br>III/DIO3                                                                   | 601038 | NM_00136<br>2 | 14q32             |
|                                                 | GNRH<br>(common to<br>all<br>gonadotropin<br>s except<br>CGH) | gonadotropin releasing hormone<br>1/LHRH/GNRH1                                                                | 152760 | NM_000825     | 8p21-p11.2        |
|                                                 |                                                               | gonadotropin releasing hormone<br>2/LHRH/GNRH2                                                                | 602352 | NM_001501     | 20p13             |
|                                                 |                                                               | gonadotropin releasing hormone<br>receptor/G protein-<br>coupled/LHRHR/GNRHR                                  | 138850 | NM_000406     | 4q21.2            |
|                                                 |                                                               | prolactin/PRL                                                                                                 | 176760 | NM_000948     | 6p22.2-p21.3      |
|                                                 | Prolactin                                                     | prolactin receptor/PRLR                                                                                       | 176761 | NM_000949     | 5p13-p12          |

|                                     |                             |                                                                                              |        |           |            |
|-------------------------------------|-----------------------------|----------------------------------------------------------------------------------------------|--------|-----------|------------|
| <b>Gonadotropin Hormones</b>        | <b>Leuteinizing Hormone</b> | cAMP responsive element binding protein 1/CREB1                                              | 123810 | NM_004379 | 2q32.3-q34 |
|                                     |                             | glycoprotein hormones, alpha polypeptide/CGAa                                                | 118850 | NM_000735 | 6q21.1-q23 |
|                                     |                             | leuteinizing hormone beta polypeptide/LHB                                                    | 152780 | NM_000894 | 19q13.32   |
|                                     |                             | luteinizing hormone/choriogonadotropin                                                       | 152790 | NM_000233 | 2p21       |
|                                     |                             | glycoprotein hormones, alpha polypeptide/CGAa                                                | 118850 | NM_000735 | 6q21.1-q23 |
|                                     |                             | follicle stimulating hormone-inhibin, beta A (activin A, activin AB alpha polypeptide)/INHBA | 136530 | AH002701  | 11p13      |
|                                     |                             | activin A receptor, type I/ACVR1                                                             | 147290 | NM_002192 | 7p15-p13   |
|                                     |                             | activin A receptor, type IB/ACVR1B                                                           | 102576 | NM_001105 | 2q23-q24   |
|                                     |                             | activin A receptor type II-like I/ACVRL1                                                     | 601300 | NM_004302 | 12q13      |
|                                     |                             | activin typeII A receptor/ACVR2                                                              | 601284 | NM_000020 | 12q11-q14  |
| <b>Follicle Stimulating Hormone</b> |                             | activin A receptor, type IIB/ACVR2B                                                          | 102581 | NM_001616 | *****      |
|                                     |                             | alpha-inhibin/INHBA                                                                          | 602730 | NM_001106 | 3p22-p21.3 |
|                                     |                             | beta-B inhibin/beta C inhibin/INHBC                                                          | 147380 | NM_001106 | 2q33-q36   |
|                                     |                             | folliculin/FST                                                                               | 601233 | NM_005538 | 12q13.1    |
|                                     |                             | follicle stimulating hormone receptor/FSHR                                                   | 136470 | NM_006350 | 5p14       |
|                                     |                             | FSH primary response (LRPR1, rat) homolog 1/FSHPRH1                                          | 136435 | NM_000145 | 2p21-p16   |
|                                     |                             |                                                                                              | 300065 | NM_006733 | Xq22       |
|                                     |                             | glycoprotein hormones, alpha polypeptide/CGAa                                                | 118850 | NM_000735 | 6q21.1-q23 |
|                                     |                             |                                                                                              |        |           |            |
|                                     |                             |                                                                                              |        |           |            |

|                                           |                                                                                                             |        |           |            |
|-------------------------------------------|-------------------------------------------------------------------------------------------------------------|--------|-----------|------------|
| <b>Chorionic Gonadotropin</b>             | chorionic gonadotropin, beta polypeptide/CGB                                                                | 118860 | NM_000737 | 19q13.32   |
|                                           | luteinizing hormone/choriogonadotropin                                                                      | 152790 | NM_000233 | 2p21       |
| <b>Anabolism</b>                          | 3-hyd oxy-3-methylglutaryl-Coenzyme A synthase 1                                                            | 142940 | NM_002130 | 5p14-p13   |
|                                           | HMGCoA reductase/HMGCR                                                                                      | 142910 | NM_000859 | 5q13.3-q14 |
|                                           | squalene synthetase/arnesyl-diphosphate farnesyltransferase                                                 | 184420 | NM_004462 | 8p23.1-p22 |
|                                           | steroid-5-alpha-reductase, alpha polypeptide 1 (3-oxo-5 alpha-steroid delta 4-dehydrogenase alpha 1)/SRD5A1 | 184753 | NM_001047 | 5p15       |
|                                           | steroid-5-alpha-reductase, alpha polypeptide 2 (3-oxo-5 alpha-steroid delta 4-dehydrogenase alpha 2)/SRD5A2 | 264600 | NM_000348 | 2p23       |
|                                           | steroidogenic acute regulatory protein/STAR                                                                 | 600617 | NM_000349 | 8p11.2     |
|                                           | cytochrome P450, subfamily XIA (cholesterol side chain cleavage)/CYP11A                                     | 118485 | NM_000781 | 15q23-q24  |
|                                           | ferredoxin 1/FDX1                                                                                           | 103260 | NM_004109 | 11q22      |
|                                           | cytochrome P450, subfamily XVII (steroid 17-alpha-hydroxylase), adrenal hyperplasia/CYP17                   | 202110 | NM_000102 | 10q24.3    |
|                                           |                                                                                                             |        |           |            |
| <b>General Steroid Hormone Metabolism</b> |                                                                                                             |        |           |            |

|                                        |                                                                                               |        |               |         |
|----------------------------------------|-----------------------------------------------------------------------------------------------|--------|---------------|---------|
| (additional<br>genes in<br>Toxicology) | hydroxy-delta-5-steroid<br>dehydrogenase, 3 beta- and steroid<br>delta-isomerase 1/HSD3B1     | 109715 | NM_00086<br>2 | 1p13.1  |
|                                        | hydroxy-delta-5-steroid<br>dehydrogenase, 3 beta- and steroid<br>delta-isomerase 2/HSD3B2     | 201810 | NM_00019<br>8 | 1p13.1  |
| <b>Catabolism</b>                      | dehydroepiandrosterone (DHEA)-<br>preferring sulfotransferase, family 2A,<br>member 1/SULT2A1 | 125263 | NM_00316<br>7 | 19q13.3 |
|                                        | estrogen-preferring                                                                           | 600043 | NM_005420     | 4q13.1  |
|                                        | UDP glycosyltransferase 1/UGT1                                                                | 191740 | NM_00107<br>2 | Chr. 12 |
|                                        | UDP glycosyltransferase family 2,<br>member B4/UGT2B4                                         | 600067 | NM_00107<br>3 | 4q13    |
|                                        | UDP glycosyltransferase family 2,<br>member B7/UGT2B7                                         | 600068 | NM_00107<br>4 | 1q14    |
|                                        | UDP glycosyltransferase 2 family,<br>polypeptide B11/UGT2B11                                  | 603064 | NM_00107<br>3 | *****   |
|                                        | UDP glycosyltransferase family 2,<br>member B15/UGT2B15                                       | 600069 | NM_00107<br>6 | 4q13    |
|                                        | UDP glycosyltransferase family 2,<br>member B17/UGT2B17                                       | 601903 | NM_00107<br>7 | 1q14    |
|                                        | hydroxy-delta-5-steroid<br>dehydrogenase, 3 beta- and steroid<br>delta-isomerase 1/HSD3B1     | 109715 | NM_00086<br>2 | 1p13.1  |
|                                        | hydroxy-delta-5-steroid<br>dehydrogenase, 3 beta- and steroid<br>delta-isomerase 2/HSD3B2     | 201810 | NM_00019<br>8 | 1p13.1  |
| <b>Synthesis</b>                       |                                                                                               |        |               |         |
|                                        |                                                                                               |        |               |         |

|                   |                   |                                                                                                             |        |            |            |
|-------------------|-------------------|-------------------------------------------------------------------------------------------------------------|--------|------------|------------|
| <b>Progestins</b> | <b>Receptors</b>  | progesterone receptor/PGR                                                                                   | 264080 | NM_000926  | 11q22      |
|                   |                   | heat shock 90-kD protein 1, alpha subunit/HSPCA                                                             | 140571 | *****      | 1q21.2-q22 |
|                   |                   | heat shock 90-kD protein 1, beta subunit/HSPCB                                                              | 140572 | J04988     | 6p12       |
|                   |                   | FK506-binding protein 5/FKBP5                                                                               | 602623 | NM_004117  | *****      |
| <b>Estrogens</b>  | <b>Synthesis</b>  | cytochrome P450, subfamily XIX (arogen aromatase)/CYP19                                                     | 107910 | NM_000103  | 15q21.1    |
|                   | <b>Receptors</b>  | estrogen receptor 1/ESR1                                                                                    | 133430 | NM_000125  | 6q25.1     |
|                   |                   | estrogen receptor 2/ESR2                                                                                    | 601663 | X99101     | 14q        |
|                   |                   | estrogen-related receptor                                                                                   | 601998 | NM_004451  | 11q12      |
|                   |                   | estrogen-related receptor beta/ESRRB                                                                        | 602167 | NM_004452  | 14q24.3    |
|                   | <b>Catabolism</b> | estrogen-preferring                                                                                         | 600043 | NM_005420  | 4q13.1     |
| <b>Androgens</b>  | <b>Synthesis</b>  | steroid-5-alpha-reductase, alpha polypeptide 1 (3-oxo-5 alpha-steroid delta 4-dehydrogenase alpha 1)/SRD5A1 | 184753 | NM_001047  | 5p15       |
|                   |                   | hydroxysteroid (17-beta) dehydrogenase 3/HSD17B3                                                            | 264300 | NM_000197  | 9q22       |
|                   |                   | cytochrome P450, subfamily XIA (cholesterol side chain cleavage)/CYP11A                                     | 118485 | NM_0000781 | 15q23-q24  |
|                   |                   | steroid 5-alpha-reductase 2/SRD5A2                                                                          | 264600 | NM_000348  | 2p23       |
|                   | <b>Receptor</b>   | androgen receptor (dihydrotestosterone receptor)/AR                                                         | 313700 | NM_000044  | Xq11-q12   |
|                   | <b>Catabolism</b> | UDP glycosyltransferase 2 family, polypeptide B17/UGT2B17                                                   | 601903 | NM_001077  | 4q13       |
|                   |                   |                                                                                                             |        |            |            |
|                   |                   |                                                                                                             |        |            |            |

|                                                  |                              |                                                                                           |        |           |            |
|--------------------------------------------------|------------------------------|-------------------------------------------------------------------------------------------|--------|-----------|------------|
| Glucocorticoids<br>(cortisol,<br>corticosterone) | Synthesis                    | cytochrome P450, subfamily XXI<br>(steroid 21-hydroxylase)/CYP21                          | 201910 | X58902    | 6p21.3     |
|                                                  |                              | cytochrome P450, subfamily XIB<br>(steroid 18-beta-hydroxylase),<br>polypeptide 2/CYP11B2 | 124080 | NM_000498 | 8q21       |
|                                                  |                              | cytochrome P450, subfamily XIB<br>(steroid 11-beta-hydroxylase),<br>polypeptide 1/CYP11B1 | 202010 | NM_000497 | 8q21       |
| Glucocorticoids<br>(cortisol,<br>corticosterone) | Receptor<br>and<br>Cofactors | glucocorticoid receptor/GRL                                                               | 138040 | NM_000176 | 5q31       |
|                                                  |                              | heat shock 70kD protein 1/HSPA1A                                                          | 140550 | NM_005345 | 6p21.3     |
|                                                  |                              | heat shock 70kD protein-like<br>1/HSPA1L                                                  | 140559 | NM_005527 | 6p21.3     |
|                                                  |                              | heat shock 70kD protein 1/HSPA1B                                                          | 603012 | NM_005346 | 6p21.3     |
|                                                  |                              | heat shock 90-kD protein 1, alpha<br>subunit/HSPCA                                        | 140571 | *****     | 1q21.2-q22 |
|                                                  |                              | heat shock 90-kD protein 1, beta<br>subunit/HSPCB                                         | 140572 | J04988    | 6p12       |
|                                                  |                              | FK506-binding protein 4<br>(59kD)/FKBP4                                                   | 600611 | NM_002014 | *****      |
|                                                  |                              | mineralocorticoid<br>receptor/MCR/nuclear receptor<br>subfamily 3, group C, member        | 600983 | NM_000901 | 4q31.1     |
|                                                  |                              | corticosteroid binding globulin<br>precursor/CBG                                          | 122500 | NM_001756 | 14q32.1    |
|                                                  |                              | hydroxy-D-5-steroid dehydrogenase, 3<br>b- and steroid D-isomerase 2/HSD3B2               | 201810 | NM_000198 | 1p13.1     |
|                                                  | Transport<br>and Catabolism  | cytochrome P450, subfamily XIB,<br>polypeptide 2 (steroid 11-b-<br>hydroxylase)/CYP11B2   | 124080 | NM_000498 | 8q21       |

|                                                            |              |                                                                              |        |           |            |
|------------------------------------------------------------|--------------|------------------------------------------------------------------------------|--------|-----------|------------|
| Mineralocorticosteroids (aldosterone, deoxycorticosterone) | Synthesis    | sodium channel, nonvoltage-gated 1 alpha/SCNN1A                              | 600228 | NM_001038 | 12p13      |
|                                                            |              | sodium channel, nonvoltage-gated 1, beta (Liddle syndrome)/SCNN1B            | 600760 | NM_000336 | 16p13-p12  |
|                                                            |              | sodium channel, nonvoltage-gated 1, gamma/SCNN1G                             | 600761 | NM_001039 | 16p13-p12  |
|                                                            |              | mineralocorticoid receptor/MCR/nuclear receptor subfamily 3, group C, member | 600983 | NM_000901 | 4q31.1     |
| Mediators of Steroid Response                              | Receptor     | nuclear receptor coactivator 2/GRIPI                                         | 601993 | NM_006540 | *****      |
|                                                            |              | oxysterol binding protein/OSBP                                               | 167040 | NM_002556 | 11q12-q13  |
|                                                            |              | sterol regulatory element binding transcription factor 1/SREBF1              | 184756 | NM_004176 | 17p11.2    |
|                                                            |              | sterol regulatory element binding transcription factor 2/SREBF2              | 600481 | NM_004599 | 22q13      |
|                                                            |              | steroid receptor coactivator 1/SRC1                                          | 602691 | NM_003743 | 2p23       |
|                                                            |              | steroid receptor RNA activator/SRA                                           | 603819 | AF092038  | Chr. 5     |
| Serotonin                                                  | Receptors    | 5-hydroxytryptamine (serotonin) receptor 2C (G protein-coupled)/HTR2C        | 312861 | NM_000868 | Xq24       |
|                                                            |              | dopamine receptor D1/DRD1                                                    | 126449 | NM_000794 | 5q35.1     |
| Dopamine                                                   | Receptors    | dopamine receptor D2/DRD2                                                    | 126450 | NM_000795 | 11q23      |
| Norepinephrine                                             | Receptors    | adrenergic, beta-2-, receptor, surface/ADRB2                                 | 109690 | NM_000024 | 5q32-q34   |
|                                                            |              | adrenergic, beta-3-, receptor/ADRB3                                          | 109691 | NM_000025 | 8p12-p11.2 |
| Neuropeptides                                              | Biosynthesis | Neuropeptide Y/NPY                                                           | 162640 | NM_000905 | 7p15.1     |
|                                                            |              | Neuropeptide Y receptor Y1/NPY1R                                             | 162641 | NM_000909 | 4q31.3-q32 |
|                                                            |              | Neuropeptide Y receptor Y2/NPY2R                                             | 162642 | NM_000910 | 4q31       |



|                                   |              |                                                                                 |        |           |              |
|-----------------------------------|--------------|---------------------------------------------------------------------------------|--------|-----------|--------------|
| Neuropeptide Y (NPY)              | Receptors    | Neuropeptide Y receptor Y3/chemokine receptor                                   | 162643 | X71635    | 2q21         |
|                                   |              | Neuropeptide Y receptor Y5/NPY5R                                                | 602001 | NM_006174 | 4q31-q32     |
|                                   |              | Neuropeptide Y receptor Y6/NPY6R                                                | 601770 | NM_006173 | 5q31         |
|                                   | Biosynthesis | preprogalanin/GALI                                                              | 137035 | L11144    | 1q13.3-q13.5 |
| Galanin                           | Receptor     | galanin receptor 1 (brain)/GALR1                                                | 600377 | NM_001480 | 18q23        |
|                                   |              | galanin receptor 2/GALR2                                                        | 603691 | NM_003857 | 17q25.3      |
|                                   |              | galanin receptor 3 (brain)/GALR3                                                | 603692 | NM_003614 | 2q12.2-q13.1 |
|                                   |              | pro-melanin-concentrating hormone/PMCH                                          | 176795 | NM_002674 | 12q23-q24    |
| Pro-Melanin Concentrating Hormone | Biosynthesis | pro-melanin-concentrating hormone-like 1/PMCHL1                                 | 176793 | *****     | 5p14         |
|                                   |              | pro-melanin-concentrating hormone-like 2/PMCHL2                                 | 176794 | AF064698  | 5q12-q13     |
|                                   |              | melanin-concentrating hormone receptor/MCHR/G protein-coupled receptor 24/GPR24 | 601751 | NM_005297 | 22q13.3      |
|                                   |              | proopiomelanocortin/POMC                                                        | 176830 | NM_000939 | 2p23.3       |
| Melanocortin                      | Receptors    | melanocortin 1 receptor (alpha melanocyte stimulating hormone receptor)/MC1R    | 155555 | NM_002386 | 16q24.3      |
|                                   |              | melanocortin 4 receptor/MC4R                                                    | 155541 | NM_005912 | 18q22        |
|                                   |              | melanocortin 5 receptor/MC5R                                                    | 600042 | NM_005913 | 18p11.2      |
|                                   |              | agouti (mouse)-signaling protein/ASIP                                           | 600201 | NM_001672 | 20q11.2      |
|                                   |              | cAMP responsive element binding protein 1/CREB1                                 | 123810 | NM_004379 | 2q32.3-q34   |

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|--------------------------------------------------|-----------------------------|--------------|----------------------------------------------------------------------------------|--------|-----------|----------------|
| Peptide<br>Hormonal<br>Regulation<br>of Appetite | Opioids                     | Biosynthesis | preproenkephalin<br>B/prodynorphin/PDYN                                          | 131340 | NM_006211 | 20pter-p12.2.1 |
|                                                  |                             | Receptors    | preproenkephalin<br>A/proenkephalin/PENK                                         | 131330 | NM_006211 | 8q23-q24       |
|                                                  | Cholecystokinin (CCK)       | Biosynthesis | opioid receptor, kappa 1/OPRK1                                                   | 165196 | NM_000912 | 8q11.2         |
|                                                  |                             | Receptors    | Cholecystokinin/CCK                                                              | 118440 | NM_000729 | 3pter-p21      |
|                                                  | Adrenocorticotropic Hormone | Biosynthesis | Cholecystokinin A receptor/CCKAR                                                 | 118444 | NM_000730 | 4p15.2-p15.1   |
|                                                  |                             | Receptors    | Cholecystokinin B receptor/CCKBR                                                 | 118445 | NM_000731 | 1p15.5-p15.4   |
|                                                  | PACAP                       | Biosynthesis | corticotropin releasing hormone/CRH                                              | 122560 | NM_000756 | 8q13           |
|                                                  |                             | Receptors    | urocortin/UCN                                                                    | 600945 | NM_003353 | Chr.2          |
|                                                  | Enterostatin                | Biosynthesis | urocortin 2/UCN2                                                                 | 604097 | AF104118  | *****          |
|                                                  |                             | Receptors    | Corticotropin releasing hormone receptor 1/CRHR1                                 | 122561 | U16273    | 17q12-q22      |
|                                                  | Insulin                     | Biosynthesis | Corticotropin releasing hormone receptor 2/CRHR2                                 | 602034 | NM_001883 | 7p21-p15       |
|                                                  |                             | Receptors    | Corticotropin releasing hormone binding protein/CRHBP                            | 122559 | NM_001882 | 5q11.2-q13.3   |
|                                                  | Leptin                      | Biosynthesis | adenylate cyclase activating polypeptide 1 (pituitary)/ADCYAP1                   | 102980 | NM_001117 | 18p11          |
|                                                  |                             | Receptors    | adenylate cyclase activating polypeptide 1 (pituitary) receptor type I/ADCYAP1R1 | 102981 | NM_001118 | 7p14           |
|                                                  | Ghrelin                     | Biosynthesis | enterostatin/colipase, pancreatic/CLPS                                           | 120105 | NM_001832 | 6pter-p21.1    |
|                                                  |                             | Receptors    | insulin/INS                                                                      | 176730 | NM_000207 | 11p15.5        |
|                                                  | PYY                         | Biosynthesis | insulin receptor/INSR                                                            | 147670 | NM_000208 | 19p13.2        |
|                                                  |                             | Receptors    | leptin/LEP                                                                       | 164160 | NM_000230 | 7q31.3         |
|                                                  | CCK                         | Biosynthesis | peroxisome proliferative activated receptor, gamma/PPARG                         | 601487 | NM_005037 | 3p25           |
|                                                  |                             | Receptors    |                                                                                  |        |           |                |

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| Leptin                     | Receptor     | leptin receptor/LEPR                                                                                     | 601007 | NM_002303 | 1p31     |
|                            | Signalling   | signal transducer and activator of transcription 3/STAT3                                                 | 102582 | NM_003150 | 17q21    |
|                            |              | signal transducer and activator of transcription 5A/STAT5A                                               | 601511 | NM_003152 | 17q11.2  |
|                            |              | signal transducer and activator of transcription 6, interleukin-4 induced/STAT6                          | 601512 | NM_003153 | 12q13    |
| Thyroid Hormone            | Biosynthesis | thyrotropin releasing hormone/TRH                                                                        | 275120 | NM_007117 | 3p       |
|                            | Receptors    | thyrotropin releasing hormone receptor/G protein coupled/TRHR                                            | 188545 | NM_003301 | 8q23     |
| Glucagon                   | Biosynthesis | paired box gene 6/PAX6                                                                                   | 106210 | NM_000280 | 11p13    |
|                            |              | preproglucagon/GCG                                                                                       | 138030 | NM_002054 | 2q36-q37 |
|                            | Receptor     | glucagon receptor/GCGR                                                                                   | 138033 | NM_000160 | 17q25    |
|                            |              | glucagon-like peptide 1                                                                                  | 138032 | NM_002062 | 6p21     |
| Glucagon-Like Polypeptides | Biosynthesis | glucagon-like peptide 2                                                                                  | 603659 | NM_004246 | 17p13.3  |
|                            |              | paired box gene 6/PAX6                                                                                   | 106210 | NM_000280 | 11p13    |
|                            | Receptors    | preproglucagon/GCG                                                                                       | 138030 | NM_002054 | 2q36-q37 |
|                            |              | glucagon-like peptide 1                                                                                  | 138032 | NM_002062 | 6p21     |
|                            | Receptors    | glucagon-like peptide-2 receptor precursor/GLP2R                                                         | 603659 | AF105367  | 17p13.3  |
|                            |              | somatostatin transcription factor 1/STF1/homeodomain transcription factor/insulin promoter factor 1/IPF1 | 600733 | NM_000209 | 13q12.1  |
|                            |              | paired box gene 6/PAX6                                                                                   | 106210 | NM_000280 | 11p13    |
|                            |              | paired box gene 4/PAX4                                                                                   | 167413 | NM_006193 | 7q32     |

| Control of Metabolism | Insulin                                                                                                                                           |        |            |            | Receptor |
|-----------------------|---------------------------------------------------------------------------------------------------------------------------------------------------|--------|------------|------------|----------|
|                       |                                                                                                                                                   |        |            |            |          |
| Biosynthesis          | Homo sapiens paired box gene                                                                                                                      | 167415 | NM_003466  | 2q12-q14   |          |
|                       | insulin/INS                                                                                                                                       | 176730 | NM_000207  | 11p15.5    |          |
|                       | neurogenic differentiation                                                                                                                        | 601724 | NM_002500  | 2q32       |          |
|                       | cAMP responsive element binding protein 1/CREB1                                                                                                   | 123810 | NM_004379  | 2q32.3-q34 |          |
|                       | lim homeobox transcription factor 1, alpha/LIMX1A                                                                                                 | 600298 | *****      | 1q22-q23   |          |
|                       | caudal type homeo box transcription factor 2/CDX2                                                                                                 | 600297 | NM_001265  | 13q12.3    |          |
|                       | purine-rich element binding protein A/PURA                                                                                                        | 600473 | NM_005859  | 5q31       |          |
|                       | ATP-binding cassette, sub-family C, member 8/ABCC8/sulfonylurea receptor (hyperinsulinemia)/SUR1                                                  | 600509 | NM_000352  | 11p15.1    |          |
|                       | ATP-binding cassette, sub-family C (C beta-cell inward rectifier subunit/BIR/potassium inwardly-rectifying channel, subfamily J, member 11/KCNJ11 | 601439 | NM_005691  | 12p12.1    |          |
|                       | carboxypeptidase E/CPE                                                                                                                            | 114855 | NM_001873  | Chr.4      |          |
| Receptor              | insulin receptor/INSR                                                                                                                             | 147670 | NM_000208  | 19p13.2    |          |
|                       | insulin receptor substrate 1/IRS1                                                                                                                 | 147545 | NM_0055544 | 2q36       |          |
|                       | insulin receptor substrate 2/IRS2                                                                                                                 | 600797 | NM_003749  | 13q34      |          |
|                       | insulin receptor substrate 4/IRS4                                                                                                                 | 603510 | NM_003604  | *****      |          |
|                       | growth factor receptor-bound protein 10/GRB10                                                                                                     | 601523 | NM_005311  | 7p12-p11.2 |          |

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|  |                     | growth factor receptor-bound protein 2/GRB2                                                              | 108355 | NM_002086 | 17q24-q25     |
|  | Signaling           | amylin/diabetes-associated peptide/DAP/islet amyloid polypeptide/IAPP                                    | 147940 | NM_000415 | 12p12.3-p12.1 |
|  | Metabolism          | insulin-degrading enzyme/IDE                                                                             | 146680 | NM_004969 | 10q23-q25     |
|  |                     | uncoupling protein 1 (mitochondrial, proton carrier)/UCP1                                                | 113730 | X51953    | 4q31          |
|  | Uncoupling Proteins | uncoupling protein 2 (mitochondrial, proton carrier)/UCP2                                                | 601693 | AF019409  | 11q13         |
|  |                     | uncoupling protein 3 (mitochondrial, proton carrier)/UCP3                                                | 602044 | NM_003356 | 11q13         |
|  |                     | uncoupling protein 4 (mitochondrial, proton carrier)/UCP4                                                | *****  | NM_004277 | *****         |
|  |                     | somatostatin transcription factor 1/STF1/homeodomain transcription factor/insulin promoter factor 1/IPF1 | 600733 | NM_000209 | 13q12.1       |
|  | Biosynthesis        | paired box gene 6/PAX6                                                                                   | 106210 | NM_000280 | 11p13         |
|  |                     | cAMP responsive element binding protein 1/CREB1                                                          | 123810 | NM_004379 | 2q32.3-q34    |
|  |                     | somatostatin/SST                                                                                         | 182450 | NM_001048 | 3q28          |
|  | Somatostatin        | preprocartistatin/CORT                                                                                   | 602784 | NM_001302 | 1p36          |
|  |                     | Somatostatin receptor 1/G protein-coupled/SSSTR1                                                         | 182451 | NM_001049 | 14q13         |
|  |                     | Somatostatin receptor 2/SSSTR2                                                                           | 182452 | NM_001050 | 17q24         |
|  |                     | Somatostatin receptor 3/adenyl cyclase coupled/SSSTR3                                                    | 182453 | NM_001051 | 22q13.1       |
|  |                     | Somatostatin receptor 4/SSSTR4                                                                           | 182454 | NM_001052 | 20p11.2       |
|  | Receptors           |                                                                                                          |        |           |               |

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|                                   |                       | Somatostatin receptor 5/SSSTR5                                    | 182455 | NM_001053 | 16p13.3      |
| <b>Growth Hormone</b>             | <b>GHRH</b>           | growth hormone releasing hormone/GHRH                             | 139190 | AH002712  | 20q11.2      |
|                                   |                       | growth hormone releasing hormone receptor/G protein-coupled/GHRHR | 139191 | NM_000823 | 7p15-p14     |
|                                   | <b>Growth Hormone</b> | growth hormone 1/somatotropin/GH1                                 | 139250 | NM_000515 | 17q22-q24    |
|                                   |                       | growth hormone receptor/GHR                                       | 60946  | NM_000163 | 5p13-p12     |
|                                   | <b>Biosynthesis</b>   | insulin-like growth factor 1 (somatomedin C)/IGF1                 | 147440 | M27544    | 12q22-q24.1  |
|                                   |                       | insulin-like growth factor 2 (somatomedin A)/IGF2                 | 147470 | NM_000612 | 11p15.5      |
|                                   | <b>Receptor</b>       | insulin-like growth factor 1 receptor precursor/IGF1R             | 147370 | NM_000875 | 15q25-q26    |
|                                   |                       | insulin-like growth factor 2 receptor/IGF2R                       | 147280 | NM_000876 | 6q26         |
| <b>Insulin-Like Growth Factor</b> | <b>Regulation</b>     | insulin-like growth factor binding protein 1/IGFBP1               | 146730 | NM_000596 | 7p14-p12     |
|                                   |                       | insulin-like growth factor binding protein 2/IGFBP2               | 146731 | M35410    | 2q33-q34     |
|                                   |                       | insulin-like growth factor binding protein 3/IGFBP3               | 146732 | NM_000598 | 7p14-p12     |
|                                   |                       | insulin-like growth factor binding protein 4/IGFBP4               | 146733 | Y12508    | 17q12-q21    |
|                                   |                       | insulin-like growth factor binding protein 5/IGFBP5               | 146734 | AF055033  | 2q33-q36     |
|                                   |                       | insulin-like growth factor binding protein 6/IGFBP6               | 146735 | M69054    | 12q13        |
|                                   |                       | insulin-like growth factor binding protein 7/IGFBP7               | 602867 | NM_001553 | 4q12         |
|                                   |                       | connective tissue growth factor/CTGF                              | 121009 | NM_001901 | 6q23.1       |
|                                   |                       | insulin-like growth factor binding protein 8/IGFBP8               | 602369 | NM_001554 | 1p22.3       |
|                                   |                       | insulin-like growth factor binding protein 9/IGFBP9               | 601489 | NM_004970 | Chr. 16      |
|                                   | <b>Catabolism</b>     | protease, serine, 11 (IGF binding)/PRSS11                         | 602194 | NM_002775 | 0q25.3-q26.2 |
|                                   |                       | heparin-binding growth factor 1/FGF1                              | 131220 | NM_000800 | 5q31         |
|                                   |                       | basic fibroblast growth factor/FGF2                               | 134920 | NM_002006 | 4q25-q27     |

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| <b>Fibroblast Growth Factor</b> | <b>Biosynthesis</b> | fibroblast growth factor 3/FGF3                                                                                                                                                                    | 164950 | NM_005247 | 11q13        |
|                                 |                     | HST oncogene/fibroblast growth factor 4/FGF4                                                                                                                                                       | 164980 | NM_002008 | 11q13        |
|                                 |                     | fibroblast growth factor-related protein/FGF5                                                                                                                                                      | 165190 | NM_004464 | 4q21         |
|                                 |                     | fibroblast growth factor 6/FGF6                                                                                                                                                                    | 134921 | X57075    | 12p13        |
|                                 |                     | keratinocyte growth factor/fibroblast growth factor 7/FGF7                                                                                                                                         | 148180 | NM_002009 | 15q15-q21.1  |
|                                 |                     | fibroblast growth factor 8 (androgen-induced)/FGF8                                                                                                                                                 | 600483 | NM_006119 | 10q24        |
|                                 |                     | fibroblast growth factor 9 (glia-activating factor)/FGF9                                                                                                                                           | 600921 | NM_002010 | 13q11-q12    |
|                                 |                     | fibroblast growth factor 10/FGF10                                                                                                                                                                  | 602115 | NM_004465 | 5p13-p12     |
|                                 |                     | fibroblast growth factor 11/FGF11                                                                                                                                                                  | 601514 | NM_004112 | 17q21        |
|                                 |                     | fibroblast growth factor 12/FGF12                                                                                                                                                                  | 601513 | *****     | 3q28         |
|                                 |                     | fibroblast growth factor 13/FGF13                                                                                                                                                                  | 300070 | NM_004114 | Xq26.3       |
|                                 |                     | fibroblast growth factor 14/FGF14                                                                                                                                                                  | 601515 | NM_004115 | 13q34        |
|                                 |                     | fibroblast growth factor 16/FGF16                                                                                                                                                                  | 603724 | NM_003868 | *****        |
|                                 |                     | fibroblast growth factor 17/FGF17                                                                                                                                                                  | 603725 | NM_003867 | 8p21         |
|                                 |                     | fibroblast growth factor 18/FGF18                                                                                                                                                                  | 603726 | NM_003862 | *****        |
|                                 |                     | fibroblast growth factor 19/FGF19                                                                                                                                                                  | 603891 | NM_005117 | *****        |
|                                 |                     | fibroblast growth factor receptor 1/FGFR1                                                                                                                                                          | 136350 | *****     | 8p11.2-p11.1 |
|                                 | <b>Receptors</b>    | fibroblast growth factor receptor 2 (bacteria-expressed kinase, keratinocyte growth factor receptor, craniofacial dysostosis 1, Crouzon syndrome, Pfeiffer syndrome, Jackson-Weiss syndrome)/FGFR2 | 176943 | NM_000141 | 10q26        |

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|                              |              | fibroblast growth factor receptor 3<br>(achondroplasia, thanatophoric<br>dwarfism)/FGFR3 | 134934 | NM_00524<br>7 | 4p16.3      |
|                              |              | fibroblast growth factor receptor<br>4/FGFR4                                             | 134935 | NM_00201<br>1 | 5q35.1-qter |
| General<br>Growth<br>Control | Signaling    | FGFR1 oncogene partner/FOP                                                               | *****  | NM_007045     | *****       |
|                              |              | suc1-associated neurotrophic factor<br>target 1 (FGFR signalling<br>adaptor)/SNT1        | *****  | NM_006654     | *****       |
|                              |              | suc1-associated neurotrophic factor<br>target 2 (FGFR signalling<br>adaptor)/SNT2        | *****  | NM_006653     | *****       |
|                              |              | sonic hedgehog (Drosophila)<br>homolog/SHH                                               | 600725 | NM_000193     | 7q36        |
|                              |              | Indian hedgehog (Drosophila)<br>homolog/IHH                                              | 600726 | L38517        | 2q33-q35    |
| Nerve<br>Growth<br>Factor    | Receptors    | patched (Drosophila) homolog/PTCH                                                        | 601309 | NM_000264     | 9q22.3      |
|                              |              | nerve growth factor, alpha<br>subunit/NGFA                                               | 162020 | *****         | *****       |
|                              |              | nerve growth factor, beta                                                                | 162030 | *****         | 1p13.1      |
|                              |              | nerve growth factor, gamma<br>subunit/NGFG                                               | 162040 | *****         | 19q13.3     |
|                              |              | nerve growth factor receptor (TNFR<br>superfamily, member 16)/NGFR                       | 162010 | NM_002507     | 17q21-q22   |
| Neurotrophins                | Biosynthesis | neurotrophin 3/NTF3                                                                      | 162660 | NM_002527     | 12p13       |
|                              |              | neurotrophin 5 (neurotrophin)                                                            | 162662 | NM_006179     | 19q13.3     |
|                              |              | neurotrophin 6, alpha/NTF6A                                                              | 604021 | NM_004149     | 19q13.3     |
|                              |              | neurotrophin 6, beta/NTF6B                                                               | 604022 | NM_004150     | 19q13.3     |
|                              |              | neurotrophin 6, gamma/NTF6G                                                              | 604023 | NM_004151     | 19q13.3     |



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| neurotrophic tyrosine kinase receptor<br>type 1/NTRK1                                      | 191315 | Y09033    | 1q21-q22      |
|                                                                                            | 600456 | NM_006180 | 9q22.1        |
|                                                                                            | 191316 | NM_002530 | 15q25         |
| neurotrophic tyrosine kinase receptor<br>type 2/NTRK2                                      | 171833 | M61906    | 5q13          |
|                                                                                            | 603157 | NM_005027 | 19q13.2-q13.4 |
|                                                                                            | *****  | NM_003629 | *****         |
| neurotrophic tyrosine kinase receptor<br>type 3/NTRK3                                      | 171834 | NM_006218 | 3q26.3        |
|                                                                                            | 602925 | NM_006219 | *****         |
|                                                                                            | 602839 | NM_005026 | 1p36.2        |
| phosphatidylinositol 3-kinase,<br>regulatory subunit, polypeptide 1 (p85,<br>alpha)/PIK3R1 | 601232 | NM_002649 | *****         |
|                                                                                            | 182530 | NM_005633 | 2p22-p21      |
|                                                                                            | 190020 | NM_005343 | 11p15.5       |
| phosphatidylinositol 3-kinase,<br>regulatory subunit, polypeptide 2 (p85,<br>beta)/PIK3R2  | 190070 | NM_004985 | 12p12.1       |
|                                                                                            |        |           |               |
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| phosphatidylinositol 3-kinase,<br>regulatory subunit, polypeptide 3 (p55,<br>gamma)/PIK3R3 |        |           |               |
|                                                                                            |        |           |               |
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| phosphoinositide-3-kinase, catalytic,<br>alpha polypeptide/PIK3CA                          |        |           |               |
|                                                                                            |        |           |               |
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| phosphoinositide-3-kinase, catalytic,<br>beta polypeptide/PIK3CB                           |        |           |               |
|                                                                                            |        |           |               |
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| phosphatidylinositol 3-kinase,<br>catalytic, delta polypeptide/PIK3CD                      |        |           |               |
|                                                                                            |        |           |               |
|                                                                                            |        |           |               |
| phosphatidylinositol 3-kinase,<br>catalytic, gamma polypeptide/PIK3CG                      |        |           |               |
|                                                                                            |        |           |               |
|                                                                                            |        |           |               |
| son of sevenless (Drosophila)<br>homolog 1/SOS1                                            |        |           |               |
|                                                                                            |        |           |               |
|                                                                                            |        |           |               |
| v-Ha-ras Harvey rat sarcoma viral<br>oncogene homolog/HRAS                                 |        |           |               |
|                                                                                            |        |           |               |
|                                                                                            |        |           |               |
| v-Ki-ras2 Kirsten rat sarcoma 2 viral<br>oncogene homolog/KRAS2                            |        |           |               |
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| <b>Mediators</b>          | neuroblastoma RAS viral (v-ras) oncogene homolog/NRAS | 164790 | NM_002524 | 1p13.2       |
|                           | Ras-related associated with diabetes/RRAD             | 179503 | NM_004165 | 16q22        |
|                           | v-raf-1 murine leukemia viral oncogene homolog 1/RAF1 | 164760 | NM_002880 | 3p25         |
| <b>Hormone Signalling</b> | mitogen activated protein kinase PRKM1/MAPK1          | 176948 | NM_002745 | 22q11.2      |
|                           | mitogen activated protein kinase PRKM3/MAPK3          | 601795 | X60188    | 16p11.2      |
|                           | mitogen activated protein kinase PRKM4/MAPK4          | 176949 | NM_002747 | 18q12-q21    |
|                           | mitogen activated protein kinase PRKM6/MAPK6          | 602904 | NM_002748 | *****        |
|                           | mitogen activated protein kinase PRKM7/MAPK7          | 602521 | NM_002749 | 17p11.2      |
|                           | mitogen activated protein kinase JNK1/PRKM8/MAPK8     | 601158 | L26318    | *****        |
|                           | mitogen activated protein kinase JNK2/PRKM9/MAPK9     | 602896 | U09759    | 5q35         |
|                           | mitogen activated protein kinase JNK3/PRKM10/MAPK10   | 602897 | U35003    | *****        |
|                           | mitogen activated protein kinase PRKM11/MAPK11        | 602898 | AF031135  | *****        |
|                           | mitogen activated protein kinase SAPK3/MAPK12         | 602399 | NM_002969 | 22q13.3      |
|                           | mitogen activated protein kinase PRKM13/MAPK13        | 602899 | NM_002754 | *****        |
|                           | mitogen activated protein kinase SAPK2A/MAPK14        | 600289 | NM_001315 | 6p21.3-p21.2 |
|                           |                                                       |        |           |              |
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| <b>Protein Kinases</b>    |                                                       |        |           |              |
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| <b>Protein<br/>Phosphatases</b> | protein tyrosine phosphatase, non-receptor type 1/PTPN1                                                          | 176885 | NM_002827 | 20q13.1-q13.2 |
|                                 | protein tyrosine phosphatase, receptor type, F/PTPRF                                                             | 179590 | NM_002840 | 1p32          |
|                                 | protein phosphatase 1, catalytic subunit, alpha isoform/PPP1CA                                                   | 176875 | NM_002708 | 11q13         |
|                                 | phogrin/IAR/receptor-like protein-tyrosine phosphatase precursor/IAR                                             | 601698 | AF007555  | 7q36          |
|                                 | protein tyrosine phosphatase, receptor type, N/PTPRN                                                             | 601773 | NM_002846 | 2q35-q36.1    |
|                                 | protein phosphatase 1, regulatory (inhibitor) subunit 2/PPP1R2                                                   | 601792 | NM_006241 | 3q29          |
| <b>Other</b>                    | insulin induced gene 1/INSIG1                                                                                    | 602055 | NM_005542 | 7q36          |
| <b>Gluconeogenesis</b>          | pyruvate carboxylase/PC                                                                                          | 266150 | NM_000920 | 11q13.4-q13.5 |
|                                 | phosphoenolpyruvate carboxykinase 1 (soluble)/PEPCK1/PCK1                                                        | 261680 | NM_002591 | 20q13.31      |
|                                 | phosphoenolpyruvate carboxykinase 2 (mitochondrial)/PEPCK2/PCK2                                                  | 261650 | NM_004563 | *****         |
|                                 | aminomethyltransferase (glycine cleavage system protein T)/AMT                                                   | 238310 | NM_000481 | 3p21.2-p21.1  |
|                                 | glycine decarboxylase<br>(decarboxylating; glycine decarboxylase, glycine cleavage system, mitochondrial, PDCD1) | 238300 | NM_000170 | 9p22          |
| <b>Glycogen Storage</b>         | glycogenin/GYG                                                                                                   | 603942 | NM_004130 | 3q24-q25.1    |
|                                 | glycogenin 2/GYG2                                                                                                | 300198 | NM_003918 | Xp22.3        |

|                                                         |                                                                                                                                                |        |               |                   |
|---------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------|--------|---------------|-------------------|
| <p><b>Regulation<br/>of Glycogen<br/>Metabolism</b></p> | glycogen synthase 1 (muscle)/GYS1                                                                                                              | 138570 | NM_00210<br>3 | 19q13.3           |
|                                                         | glycogen synthase 1 (liver)/GYS2                                                                                                               | 138571 | AJ003087      | 12p12.2           |
|                                                         | phosphorylase kinase, alpha 1<br>(muscle), muscle                                                                                              | 311870 | NM_00263<br>7 | Xq13              |
|                                                         | phosphorylase kinase, alpha 2 (liver),<br>glycogen storage disease IX/PHKA2                                                                    | 306000 | NM_00029<br>2 | Xp22.2-<br>p22.1  |
|                                                         | phosphorylase kinase, beta/PHKB                                                                                                                | 172490 | NM_000293     | 16q12-q13.1       |
|                                                         | phosphorylase kinase, gamma 2 (testis)                                                                                                         | 172471 | NM_000294     | 6p12.1-p11.2      |
|                                                         | protein phosphatase 1, regulatory<br>(inhibitor) subunit 3 (glycogen and<br>sarcoplasmic reticulum binding<br>subunit, skeletal muscle)/PPP1R3 | 600917 | NM_00271<br>1 | *****             |
|                                                         | albumin proximal factor/transcription<br>factor 1/TCF1/hepatic nuclear<br>factor/HNF1                                                          | 142410 | NM_00054<br>5 | 12q24.2           |
|                                                         | transcription factor 2/TCF2/hepatic<br>nuclear factor 2/HNF2                                                                                   | 189907 | NM_00648<br>1 | 17cen-q21.3       |
|                                                         | hepatocyte nuclear factor 3,<br>alpha/HNF3A                                                                                                    | 602294 | NM_00449<br>6 | 14q12-q13         |
|                                                         | hepatocyte nuclear factor-3<br>beta/HNF3B                                                                                                      | 600288 | AF176110      | 20p11             |
|                                                         | hepatocyte nuclear factor 3,<br>gamma/HNF3G                                                                                                    | 602295 | NM_00449<br>7 | 19q13.2-<br>q13.4 |
|                                                         | hepatocyte nuclear factor 4,<br>alpha/HNF4A                                                                                                    | 600281 | NM_00045<br>7 | 20q12-<br>q13.1   |
|                                                         | hepatocyte nuclear factor 6/HNF6                                                                                                               | 604164 | AH007195      | 15q21.1-<br>q21.2 |

| Metabolism                          | Uptake             | insulin-regulated syntaxin 4 binding protein/SYNIP                                         | *****  | *****     | *****         |
|-------------------------------------|--------------------|--------------------------------------------------------------------------------------------|--------|-----------|---------------|
|                                     |                    | glucose-6-phosphatase, transport (glucose-6-phosphate) protein 1                           | 602671 | NM_001467 | 11q23         |
| Carbohydrate Metabolism and Storage | Uptake             | Solute carrier family 5, member 1/SLC5A1/SGLT1 (glucose)                                   | 182380 | AH005284  | 22q13.1       |
|                                     |                    | Solute carrier family 2 (facilitated glucose transporter), member 1/SLC2A1/GLUT1 (glucose) | 138140 | NM_006516 | 1p35-p31.3    |
|                                     |                    | Solute carrier family 2, member 2/SLC2A2/GLUT2 (glucose)                                   | 138160 | *****     | 3q26.1-q26.3  |
|                                     |                    | Solute carrier family 2, member 3/SLC2A3/GLUT3 (glucose)                                   | 138170 | M20681    | 12p13.3       |
|                                     |                    | Solute carrier family 2, member 4/SLC2A4/GLUT4 (glucose)                                   | 138190 | NM_001042 | 17p13         |
|                                     |                    | Solute carrier family 2, member 5/SLC2A5/GLUT5 (glucose)                                   | 138230 | NM_003039 | 1p36.2        |
|                                     | Glycogen Breakdown | phosphorylase, glycogen, muscle (McArdle syndrome, glycogen storage disease type V)/PYGM   | 232600 | NM_005609 | 11q13         |
|                                     |                    | phosphorylase, glycogen; liver (Hers disease, glycogen storage disease type VI)/PYGL       | 232700 | NM_002863 | 14q21-q22     |
|                                     |                    | phosphorylase, glycogen; brain, nuclear gene encoding mitochondrial protein/PYGB           | 138550 | NM_002862 | 20p11.2-p11.1 |
|                                     |                    | glucosylase, alpha, acid (ompa disease, glycogen storage disease type VII)/PYGA            | 232300 | NM_000152 | 17q25.2-q25.3 |

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|------------------------------------------------------------------------------------------------------------------------|--------|-----------|--------------|
| amylo-1,6-glucosidase, 4-alpha-glucanotransferase (glycogen debranching enzyme, glycogen storage disease type III)/AGL | 232400 | NM_000642 | 1p21         |
| hexokinase 2, nuclear gene encoding mitochondrial protein/HK2                                                          | 601125 | NM_000189 | 2p12         |
| glucokinase (hexokinase 4, maturity onset diabetes of the young 2) nuclear gene encoding mitochondrial protein/GCK     | 138079 | NM_000162 | 7p15-p13     |
| phosphofructokinase, muscle/PFKM                                                                                       | 232800 | NM_000289 | 12q13.3      |
| pyruvate kinase, muscle/PKM2                                                                                           | 179050 | NM_002654 | 15q22        |
| pyruvate kinase, liver/PKL                                                                                             | *****  | D13243    | *****        |
| pyruvate dehydrogenase (lipoamide) alpha 1/PDHA1                                                                       | 312170 | NM_000284 | Xp22.2-p22.1 |
| pyruvate dehydrogenase (lipoamide) al                                                                                  | 179061 | NM_005390 | 4q22-q23     |
| pyruvate dehydrogenase (lipoamide) be                                                                                  | 179060 | NM_000925 | 3p13-q23     |
| pyruvate dehydrogenase dihydrolipoam                                                                                   | 246900 | NM_000108 | 7q31-q32     |
| pyruvate dehydrogenase lipoyl-contain                                                                                  | 245349 | NM_003477 | 11p13        |
| beta-galactosidase/GLB1                                                                                                | 230500 | M22590    | 3p21.33      |
| cathepsin A/CSTA/protective protein for beta-galactosidase (galactosialidosis)/PPGB                                    | 256540 | NM_000308 | 20q13.1      |

## Glycolysis

|                                                                        |                                                    |                                                                                                                                 |        |           |              |
|------------------------------------------------------------------------|----------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------|--------|-----------|--------------|
| Glycolytic<br>(and Other)<br>Protein<br>Maturation<br>and<br>Targeting | Lysosomal<br>Targeting of<br>Glycolytic<br>Enzymes | amyloid precursor protein<br>secretase/cathepsin B/CTSB                                                                         | 116810 | NM_001908 | 8p22         |
|                                                                        |                                                    | dipeptidyl-peptidase I/DPPI/cathepsin<br>C/CTSC                                                                                 | 602365 | NM_001814 | 1q14.1-q14.2 |
|                                                                        |                                                    | cathepsin D (lysosomal aspartyl/<br>protease)/CTSD                                                                              | 116840 | NM_001909 | 11p15.5      |
|                                                                        |                                                    | cathepsin E/CTSE                                                                                                                | 116890 | NM_001910 | 1q31         |
|                                                                        |                                                    | cathepsin F/CTSF                                                                                                                | 603539 | AF132894  | 11q13        |
|                                                                        |                                                    | cathepsin G/CTSG                                                                                                                | 116830 | NM_001911 | 14q11.2      |
|                                                                        |                                                    | granzyme H/GZMH/cathepsin G-like<br>2/CSTGL2                                                                                    | 116831 |           | 14q11.2      |
|                                                                        |                                                    | cathepsin H/CTSH                                                                                                                | 116820 | NM_004390 | 15q24-q25    |
|                                                                        |                                                    | cathepsin K (pseudodysostosis)/CTSK                                                                                             | 601105 | NM_000396 | 1q21         |
|                                                                        |                                                    | cathepsin L/CTSL                                                                                                                | 116880 | NM_001912 | 9q21-q22     |
|                                                                        |                                                    | cathepsin L2/CTSL2                                                                                                              | *****  | NM_001333 | *****        |
|                                                                        |                                                    | cathepsin O/CTSO                                                                                                                | 600550 | NM_001334 | 4q31-q32     |
|                                                                        |                                                    | cathepsin S/CTSS                                                                                                                | 116845 | NM_004079 | 1q21         |
|                                                                        |                                                    | cathepsin U/CTSU                                                                                                                | *****  | AF070448  | *****        |
|                                                                        |                                                    | cathepsin V/CTSV                                                                                                                | *****  | AB001928  | *****        |
|                                                                        |                                                    | cathepsin W/CTSW                                                                                                                | 602364 | NM_001335 | 11q13.1      |
|                                                                        |                                                    | cathepsin X precursor/CSTX                                                                                                      | *****  | AF073890  | *****        |
|                                                                        |                                                    | cathepsin Z/CTSZ                                                                                                                | 603169 | NM_001336 | 20q13        |
|                                                                        |                                                    | mannosyltransferase polypeptide 1                                                                                               | 603503 | NM_003859 | *****        |
|                                                                        |                                                    | mannosyltransferase polypeptide 2                                                                                               | 603564 | NM_003863 | *****        |
|                                                                        |                                                    | dolichyl-phosphate (UDP-N-<br>acetylglucosamine) N-<br>acetylglucosaminophosphotransferase<br>1 (GlcNAc-1-P transferase)/DPAGT1 | 191350 | NM_001382 | 11q23.3      |

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|------------------------------------------------------------|-----------------------------------------------------------------------------------------|--------|-----------|--------------|
| <b>Protein Glycosylation (enzymatic and non-enzymatic)</b> | aldose reductase/aldo-keto reductase family 1, member A1 (aldehyde reductase)/AKR1A1    | 103880 | NM_006066 | 7q35         |
|                                                            | sorbitol dehydrogenase/SORD                                                             | 182500 | NM_003104 | 15q15.3      |
| <b>Sugar and Transition Metal Metabolism</b>               | glutamine-fructose-6-phosphate transaminase 1/GFPT1                                     | 138292 | NM_002056 | 2p13         |
|                                                            | glutamine-fructose-6-phosphate transaminase 2/GFPT2                                     | 603865 | NM_005110 | 5q34-q35     |
|                                                            | receptor for advanced glycation end products/RAGE/AGER                                  | 600214 | AJ133822  | 6p21.3       |
|                                                            | glutamate-cysteine ligase (gamma-glutamylcysteine synthetase), catalytic (72.8kD)/GLCLC | 230450 | NM_001498 | 6p12         |
|                                                            | glutathione synthetase/GSS                                                              | 601002 | NM_000178 | 20q11.2      |
|                                                            | ATP-binding cassette 7 (iron transporter)/ABCB7                                         | 300135 | NM_004299 | Xq13.1-q13.3 |
|                                                            | transferrin/TF                                                                          | 190000 | NM_001063 | 3q21         |
|                                                            | hepatocyte growth factor/HGF                                                            | 142409 | G_HUMHG   | 7q21.1       |
|                                                            | hepatocyte growth factor receptor/oncogene MET/MET/HGFR                                 | 164860 | NM_000245 | 7q31         |
|                                                            | vascular endothelial growth factor/VEGFA                                                | 192240 | NM_003376 | 6p12         |
|                                                            | vascular endothelial growth factor/VEGFB                                                | 601398 | NM_003377 | 11q13        |
|                                                            | vascular endothelial growth factor/VEGFC                                                | 601528 | NM_005429 | *****        |
|                                                            | VEGF receptor/VEGFR                                                                     | 191306 | AF063657  | 4q12         |



|                    |                                        |                                                                                                   |        |           |               |
|--------------------|----------------------------------------|---------------------------------------------------------------------------------------------------|--------|-----------|---------------|
| Neovascularization | Vascular Growth Factors and Inhibitors | growth hormone/GHI                                                                                | 139250 | NM_000515 | 17q22-q24     |
|                    |                                        | growth hormone receptor/GHR                                                                       | 600946 | NM_000163 | 5p13-p12      |
|                    |                                        | pigment epithelium-derived                                                                        | 172860 | NM_002615 | 17p13.3       |
|                    |                                        | angiostatin/plasminogen/PLG                                                                       | 173350 | NM_000301 | 6q26          |
|                    |                                        | endostatin/type XVIII                                                                             |        |           |               |
|                    |                                        | collagen/COL18A1                                                                                  | 120328 | AF018081  | 21q22.3       |
|                    |                                        | endothelin 1/EDN1                                                                                 | 131240 | NM_001955 | 6p24-p23      |
|                    |                                        | endothelin 2/EDN2                                                                                 | 131241 | NM_001956 | 1p34          |
|                    |                                        | endothelin 3/EDN3                                                                                 | 131242 | NM_000114 | 20q13.2-q13.3 |
|                    |                                        | endothelin A receptor isoform delta                                                               |        |           |               |
|                    |                                        | 3/EDNRA                                                                                           | 131243 | AF014826  | Chr.4         |
|                    |                                        | endothelin receptor type B/EDNRB                                                                  | 131244 | NM_000115 | 13q22         |
|                    |                                        | protein kinase C beta/PRKCB                                                                       | 176970 | X06318    | 16p11.2       |
|                    |                                        | transforming growth factor, beta-1/TGFB1                                                          | 190180 | M60315    | 9q13.1-q13.3  |
|                    |                                        | transforming growth factor, beta-2/TGFB2                                                          | 190220 | NM_003238 | 1q41          |
|                    |                                        | transforming growth factor, beta-3/TGFB3                                                          | 190230 | NM_003239 | 14q24         |
|                    |                                        | transforming growth factor, beta receptor I (activin A receptor type II-like kinase, 53kD)/TGFBRI | 190181 | NM_004612 | 9q33-q34      |
|                    |                                        | transforming growth factor, beta receptor II (70-80kD)/TGFBRII                                    | 190182 | NM_003242 | 3p22          |
|                    |                                        | transforming growth factor, beta receptor III (betaglycan, 200kD)/TGFBRIII                        | 600742 | NM_003243 | 1p33-p32      |
|                    |                                        | decorin/DCN                                                                                       | 125255 | NM_001920 | 12q23         |
|                    |                                        | Munc13                                                                                            | *****  | AF020202  | *****         |

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| Hypertension<br>(hypoxia,<br>vascular<br>endothelium<br>thickening,<br>and<br>hypertension) | Ion Pump               | transient receptor potential channel 3<br>(diacylglycerol-activated non-selective<br>cation channel)/TRPC3 | 602345 | NM_003305 | *****     |
|                                                                                             |                        | transient receptor potential channel 6<br>(diacylglycerol-activated non-selective<br>cation channel)/TRPC6 | 603652 | NM_004621 | 11q21-q22 |
|                                                                                             |                        | solute carrier family 12, member<br>3/SLC12A3 (renal sodium/chloride<br>transporter)                       | 600968 | NM_000339 | 16q13     |
|                                                                                             | Angiotensin            | renin/REN                                                                                                  | 179820 | NM_000537 | Xq28      |
|                                                                                             |                        | renin-binding protein/RENP                                                                                 | 312420 | NM_002910 | 1q32      |
|                                                                                             |                        | angiotensinogen/AGT                                                                                        | 106150 | NM_000029 | 1q42-q43  |
|                                                                                             |                        | angiotensin II type 1 receptor/AGTR1                                                                       | 106165 | M87290    | 3q21-q25  |
|                                                                                             |                        | guanine nucleotide binding protein (G<br>protein), beta polypeptide 3/GNB3                                 | 139130 | NM_002075 | 12p13     |
|                                                                                             |                        | dipeptidyl carboxypeptidase I<br>(angiotensin I converting<br>enzyme)/ACE/DCPI                             | 106180 | NM_000789 | 17q23     |
|                                                                                             | Natriuretic<br>Peptide | atrial natriuretic peptide precursor<br>A/NPPA                                                             | 108780 | X01471    | 1p36.2    |
|                                                                                             |                        | atrial natriuretic peptide precursor<br>B/NPPB                                                             | 600295 | *****     | 1p36.2    |
|                                                                                             |                        | atrial natriuretic peptide precursor<br>C/NPPC                                                             | 600296 | D28874    | 2q24-qter |
|                                                                                             |                        | natriuretic peptide receptor<br>A/ANPRA/NPR1                                                               | 108960 | *****     | 1q21-q22  |
|                                                                                             |                        | natriuretic peptide receptor<br>B/ANPRB/NPR2                                                               | 108961 | *****     | 9p21-p12  |

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|-----------------------------------------------------------------------------|--------------------------------------------|-------------------------------------------------------------------------------------------------------|-----------|-------------|---------------|
| Blood Pressure Regulation<br>(additional genes in Cardiovascular and Renal) |                                            | natriuretic peptide receptor C/ANPRC/NPR3                                                             | 108962    | NM_000908   | 5p14-p12      |
|                                                                             | Endothelin                                 | endothelin 1/EDN1                                                                                     | 131240    | NM_001955   | 6p24-p23      |
|                                                                             |                                            | endothelin 2/EDN2                                                                                     | 131241    | NM_001956   | 1p34          |
|                                                                             |                                            | endothelin 3/EDN3                                                                                     | 131242    | NM_000114   | 20q13.2-q13.3 |
|                                                                             |                                            | endothelin converting enzyme 1/ECE1                                                                   | 600423    | NM_001397   | 1p36.1        |
|                                                                             |                                            | endothelin A receptor isoform delta 3/EDNRA                                                           | 131243    | AF014826    | Chr.4         |
|                                                                             | Vasopressin                                | endothelin receptor type B/EDNRB                                                                      | 131244    | NM_000115   | 13q22         |
|                                                                             |                                            | arginine vasopressin (neurophysin II, antidiuretic hormone, diabetes insipidus, neurohypophyseal)/AVP | 192340    | NM_000490   | 20p13         |
|                                                                             |                                            | arginine vasopressin receptor 1A/AVPR1A                                                               | 600821    | NM_000706   | 12q14-q15     |
|                                                                             |                                            | arginine vasopressin receptor 1B/AVPR1B                                                               | 600264    | NM_000707   | 1q32          |
|                                                                             |                                            | arginine vasopressin receptor 2 (nephrogenic diabetes leucyl/cystinyl)                                | 304800    | NM_000054   | Xq28          |
|                                                                             |                                            |                                                                                                       | 151300    | NM_005575   | *****         |
|                                                                             |                                            | nitric oxide synthetase 1/NOS1                                                                        | 163731    | AH001515    | 2q24.2-q24.3  |
|                                                                             |                                            | nitric oxide synthetase 2A/NOS2A                                                                      | 163730    | X85766      | 17cen-q11.2   |
|                                                                             |                                            | macrophage nitric oxide synthetase 2B/NOS2B                                                           | 600719    | AH006623    | 17p13.1-q25   |
| macrophage nitric oxide synthetase 2C/NOS2C                                 |                                            | 600720                                                                                                | 600720    | 17p13.1-q25 |               |
| nitric oxide synthetase 3/NOS3                                              | 163729                                     | AH001515                                                                                              | 7q36      |             |               |
| Nitric Oxide Pathway<br>(additional Genes in Cardiovascular and Renal)      | chondrocyte nitric oxide synthetase 3/NOS4 | 163728                                                                                                | X73029    | *****       |               |
|                                                                             | arginase/ARG1                              | 207800                                                                                                | NM_000045 | *****       |               |

|                                         | arginase/ARG2                                                                                        | 107830 | NM_001172 | 4q24.1-q24.3 |
|-----------------------------------------|------------------------------------------------------------------------------------------------------|--------|-----------|--------------|
| <b>Ion Channels</b>                     | ATP sensitive potassium inwardly-rectifying channel, subfamily J, member 5/KCNJ5                     | 600734 | NM_000890 | 11q24        |
|                                         | transient receptor potential channel 3 (diacylglycerol-activated non-selective cation channel)/TRPC3 | 602345 | NM_003305 | *****        |
|                                         | transient receptor potential channel 6 (diacylglycerol-activated non-selective cation channel)/TRPC6 | 603652 | NM_004621 | 11q21-q22    |
|                                         | potassium large conductance calcium-activated channel, subfamily M, alpha member 1/KCNMA1            | 600150 | NM_002247 | 10q22        |
|                                         | potassium large conductance calcium-activated channel, subfamily M, beta member 1/KCNMB1             | 603951 | NM_004137 | 5q34         |
|                                         | superoxide dismutase 1/SOD1                                                                          | 147450 | NM_000454 | 21q22.1      |
|                                         | superoxide dismutase 2, mitochondrial                                                                | 147460 | X65965    | 6q25.3       |
|                                         | glutamate-cysteine ligase (gamma-glutamylcysteine synthetase), catalytic (72.8kD)/GLCLC              | 230450 | NM_001498 | 6p12         |
|                                         | glutathione synthetase/GSS                                                                           | 601002 | NM_000178 | 20q11.2      |
|                                         | catalase/CAT                                                                                         | 115500 | NM_001752 | 11p13        |
| <b>Amelioration of Oxidative Stress</b> | <b>Antioxidants and Free Radical Scavengers</b>                                                      |        |           |              |
|                                         | glutathione peroxidase 1/GPX1                                                                        | 138320 | AF029317  | 3p21.3       |
|                                         | glutathione peroxidase 2 (gastrointestinal)/GPX2                                                     | 138319 | NM_002083 | 14q24.1:     |

|           |                                                                     |        |           |               |
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|           | glutathione peroxidase 3 (plasma)/GPX3                              | 138321 | NM_002084 | 5q32-q33.1    |
|           | glutathione peroxidase 4 (phospholipid hydroperoxidase)/GPX4        | 138322 | NM_002085 | 19p13.3       |
|           | glutathione peroxidase 5 (epididymal androgen-related protein)/GPX5 | 603435 | NM_001509 | *****         |
|           | apolipoprotein (a), Lp(a)/LPA                                       | 152200 | NM_005577 | 6q27          |
| Transport | RBP5/cellular retinoic acid-binding protein 1/CRABP1                | 180230 | NM_004378 | 15q24         |
|           | cellular retinoic acid-binding protein 2/CRABP2                     | 180231 | NM_001878 | 1q21.3        |
|           | retinol-binding protein 1,                                          | 180260 | NM_002899 | 3q21-q22      |
|           | retinol-binding protein 2,                                          | 180280 | NM_004164 | 3q21-qter     |
|           | retinol-binding protein 3, interstitial/RBP3                        | 180290 | NM_002900 | 10q11.2       |
|           | retinol-binding protein 4, interstitial/RBP4                        | 180250 | NM_006744 | 10q24         |
|           | serum vitamin D-binding protein/DBP/group-specific component/GC     | 139200 | L10641    | 4q12          |
|           | transthyretin (prealbumin, amyloidosis type I)/TTR                  | 176300 | NM_000371 | 18q11.2-q12.1 |
|           | Retinoic acid receptor, alpha/RARA                                  | 180240 | NM_000964 | 17q12         |
|           | Retinoic acid receptor, beta/RARB                                   | 180220 | NM_000965 | 3p24          |
|           | Retinoic acid receptor, gamma/RARG                                  | 180190 | NM_000966 | 12q13         |

|                   |                                   |                                                                    |        |           |             |
|-------------------|-----------------------------------|--------------------------------------------------------------------|--------|-----------|-------------|
| <b>Retinoids</b>  | <b>Receptors and Coactivators</b> | Retinoid X receptor alpha/RXRA                                     | 180245 | NM_005693 | 9q34.3      |
|                   |                                   | Retinoid X receptor beta/RXRB                                      | 180246 | X66424    | 6p21.3      |
|                   |                                   | Retinoid X receptor gamma/RXRG                                     | 180247 | U38480    | 1q22-q23    |
|                   |                                   | RAR-related orphan receptor A/RORA                                 | 600825 | NM_002943 | 15q21-q22   |
|                   |                                   | RAR-related orphan receptor B/RORB                                 | 601972 | *****     | 15q21-q22   |
|                   |                                   | RAR-related orphan receptor C/RORC                                 | 602943 | NM_005060 | 1q21        |
|                   |                                   | nuclear receptor coactivator 2/GRIP1                               | 601993 | NM_006540 | *****       |
|                   |                                   | silencing mediator for retinoid and thyroid hormone receptors/SMRT | 600848 | NM_006312 | *****       |
|                   |                                   | retinoic and thyroid hormone receptor associated corepressor       |        |           |             |
|                   |                                   | 1/TRAC1/NCOR1                                                      | 600849 | NM_006311 | *****       |
| <b>Catabolism</b> |                                   | UDP glycosyltransferase 1/UGT1                                     | 191740 | NM_001072 | Chr. 12     |
|                   |                                   | UDP glycosyltransferase family 2, member B4/UGT2B4                 | 600067 | NM_001073 | 4q13        |
|                   |                                   | UDP glycosyltransferase family 2, member B7/UGT2B7                 | 600068 | NM_001074 | 1q14        |
|                   |                                   | UDP glycosyltransferase 2 family, polypeptide B11/UGT2B11          | 603064 | NM_001073 | *****       |
|                   |                                   | UDP glycosyltransferase family 2, member B15/UGT2B15               | 600069 | NM_001076 | 4q13        |
|                   |                                   | UDP glycosyltransferase family 2, member B17/UGT2B17               | 601903 | NM_001077 | 1q14        |
|                   |                                   | Peroxisome proliferative activated receptor, alpha/PPARA           | 170998 | NM_005036 | 22q12-q13.1 |

**Adipocyte  
Differentiation**

|                          |                                                                               |                                                                               |           |            |               |
|--------------------------|-------------------------------------------------------------------------------|-------------------------------------------------------------------------------|-----------|------------|---------------|
| Peroxisome Proliferation | Receptors and Coactivators                                                    | Peroxisome proliferative activated receptor, delta/PPARD                      | 6E+05     | NM_006238  | 1q21.3        |
|                          |                                                                               | peroxisome proliferative activated receptor, gamma/PPARG                      | 601487    | NM_005037  | 3p25          |
|                          |                                                                               | CCAAT/enhancer binding protein (C/EBP), alpha/CEBPA                           | 116897    | NM_004364  | 19q13.1       |
|                          |                                                                               | CCAAT/enhancer binding protein (C/EBP), beta/CEBPB                            | 189965    | NM_005194  | 20q13.1       |
|                          |                                                                               | CCAAT/enhancer binding protein (C/EBP), gamma/CEBPG                           | 138972    | NM_001806  | Chr. 19       |
|                          |                                                                               | CCAAT/enhancer binding protein (C/EBP), delta/CEBPD                           | 116898    | NM_005195  | 8p11.2-p11.1  |
|                          |                                                                               | CCAAT/enhancer binding protein (C/EBP), epsilon/CEBPE                         | 600749    | NM_001805  | 14q11.2       |
|                          |                                                                               | acetyl-Coenzyme A carboxylase alpha/ACACA                                     | 200350    | NM_000664  | 17q21         |
|                          |                                                                               | acetyl-Coenzyme A carboxylase beta/ACACB                                      | 601557    | NM_001093  | 12q24.1       |
|                          |                                                                               | acetyl-Coenzyme A acetyltransferase 1 (acetoacetyl Coenzyme A thiolase)/ACAT1 | 203750    | NM_000019  | 11q22.3-q23.1 |
| Biosynthesis             | acetyl-Coenzyme A acetyltransferase 2 (acetoacetyl Coenzyme A thiolase)/ACAT2 | 100678                                                                        | NM_005891 | 6q25.3-q26 |               |
|                          | ATP citrate lyase/ACLY                                                        | 108728                                                                        | NM_001096 | 17q21.1    |               |
|                          | glycerol-3-phosphate acyltransferase, mitochondrial/GPAM1                     | 602395                                                                        | *****     | 10q24-q26  |               |
|                          | fatty acid synthase/FASN                                                      | 600212                                                                        | NM_004104 | 17q25      |               |

|                  |                                                                                  |        |           |              |
|------------------|----------------------------------------------------------------------------------|--------|-----------|--------------|
| <b>Transport</b> | apolipoprotein A1 of HDL/APOA1                                                   | 107680 | NM_000039 | 11q23        |
|                  | apolipoprotein A2/APOA2                                                          | 107670 | NM_001643 | 1q21-q23     |
|                  | apolipoprotein A4/APOA4                                                          | 107690 | NM_000482 | 11q23        |
|                  | apolipoprotein B (including Ag(x) antigen)/APOB                                  | 107730 | NM_000384 | 2p24         |
|                  | apolipoprotein B mRNA editing enzyme, catalytic polypeptide                      | 600130 | NM_005889 | 12p13.1      |
|                  | APOBEC1 binding protein/ABBP1/heterogeneous nuclear ribonucleoprotein A/B/HNRPAB | 602688 | NM_004499 | *****        |
|                  | apolipoprotein C1/APOC1                                                          | 107710 | NM_001645 | 19q13.2      |
|                  | apolipoprotein C2/APOC2                                                          | 207750 | NM_000483 | 19q13.2      |
|                  | apolipoprotein C3/APOC3                                                          | 107720 | NM_000040 | 11q23        |
|                  | apolipoprotein C4/APOC4                                                          | 600745 | NM_001646 | 19q13.2      |
|                  | apolipoprotein D/APOD                                                            | 107740 | NM_001647 | 3q26.2-qter  |
|                  | apolipoprotein E/APOE                                                            | 107741 | NM_000041 | 19q13.2      |
|                  | apolipoprotein F/APOF                                                            | 107760 | NM_001638 | Chr.12       |
|                  | apolipoprotein H (beta-2-glycoprotein I)/APOH                                    | 138700 | NM_000042 | 17q23-qter   |
|                  | apolipoprotein J/clustrin/APOJ/CLU                                               | 185430 | NM_001831 | 8p21-p12     |
|                  | apolipoprotein L/APOL                                                            | 603743 | AF019225  | Chr. 22      |
|                  | pancreatic triglyceride lipase/PNLIP                                             | 246600 | AH003527  | 10q26.1      |
|                  | enterostatin/colipase, pancreatic/CLPS                                           | 120105 | NM_001832 | 6pter-p21.1  |
|                  | low density lipoprotein receptor (familial hypercholesterolemia)/LDLR            | 143890 | NM_000527 | 9p13.2-p13.1 |
|                  | low density lipoprotein receptor-related protein 1/LRP1                          | 107770 | NM_002332 | 2q13.1-q13.2 |
|                  | low density lipoprotein receptor-related protein 2/LRP2                          | 600073 | U33837    | 2q24-q31     |



| Lipid Metabolism and Storage |  | Lipid Metabolism and Storage                                        |        |           |              |  |
|------------------------------|--|---------------------------------------------------------------------|--------|-----------|--------------|--|
| Uptake                       |  | low density lipoprotein receptor-related protein 5/LRP5             | 603506 | AF077820  | 11q13.4      |  |
|                              |  | low density lipoprotein receptor-related protein 8/LRP8             | 602600 | NM_004631 | 1p34         |  |
|                              |  | low density lipoprotein receptor-related protein-associated protein | 104225 | NM_002337 | 4p16.3       |  |
|                              |  | oxidized low density lipoprotein receptor/OLR1                      | 602601 | NM_002543 | 12p13-p12    |  |
|                              |  | very low density lipoprotein receptor/VLDLR                         | 192977 | NM_003383 | 9p24         |  |
|                              |  | microsomal triglyceride transfer protein large subunit/MTP          | 157147 | NM_000253 | 4q22-q24     |  |
|                              |  | sortilin related receptor/SORL1                                     | 602005 | NM_003105 | 1q23.2-q24.2 |  |
|                              |  | plasma cholesterol ester transfer protein/CETP                      | 118470 | NM_000078 | 16q21        |  |
|                              |  | phospholipid transfer protein/PLTP                                  | 172425 | NM_006227 | 20q12-q13.1  |  |
| Storage                      |  | glycerol-3-phosphate acyltransferase, mitochondrial/GPAM1           | 602395 | *****     | 10q24-q26    |  |
| Release                      |  | lipoprotein lipase/LPL                                              | 238600 | NM_000237 | 8p22         |  |
|                              |  | lipase, hepatic/LIPC                                                | 151670 | NM_000236 | 15q21-q23    |  |
|                              |  | adrenergic, beta-3-, receptor/ADRB3                                 | 109691 | NM_000025 | 8p12-p11.2   |  |
|                              |  | lysosomal acid lipase/LIPB                                          | 278000 | NM_000235 | 10q24-q25    |  |
|                              |  | lipase, hormone-sensitive/LIPE                                      | 151750 | NM_005357 | 9q13.1-q13.2 |  |
|                              |  | perilipin/PLIN                                                      | 170290 | NM_002666 | 15q26        |  |
|                              |  | fatty acid binding protein 4, adipocyte/FABP4                       | 600434 | NM_001442 | 8q21         |  |
|                              |  | Fatty acid CoA Ligase, long chain 1/FACL1                           | 152425 | *****     | 3q13         |  |

|                           |                                                                                                |        |               |            |
|---------------------------|------------------------------------------------------------------------------------------------|--------|---------------|------------|
| <b>Coenzyme A Ligases</b> | Fatty acid CoA Ligase, long chain 2/FACL2                                                      | 152426 | *****         | 4q34-q35   |
|                           | Fatty acid CoA Ligase, long chain 3/FACL3                                                      | 602371 | NM_00445<br>7 | 2q34-q35   |
|                           | Fatty acid CoA Ligase, long chain 4/FACL4                                                      | 300157 | NM_00445<br>8 | Xq22.3     |
|                           | Fatty acid CoA Ligase, very long chain 1/FACVL1                                                | 603247 | NM_00364<br>5 | 15q21.2    |
| <b>β-Oxidation</b>        | acyl-Coenzyme A dehydrogenase, long                                                            | 201460 | NM_001608     | 2q34-q35   |
|                           | acyl-Coenzyme A dehydrogenase, C-4                                                             | 201450 | NM_000016     | 1p31       |
|                           | acyl-Coenzyme A dehydrogenase, C-2                                                             | 201470 | NM_000017     | 12q22-qter |
|                           | carnitine palmitoyltransferase I, liver, nuclear gene encoding mitochondrial protein/CPT1A     | 600528 | NM_001876     | 11q13      |
|                           | carnitine palmitoyltransferase II, nuclear gene encoding mitochondrial protein/CPT2            | 600650 | NM_000098     | 1p32       |
|                           | carnitine/acylcarnitine                                                                        | 212138 | NM_000387     | 3p21.31    |
|                           | Enoyl-CoA, hydratase/3-hydroxyacyl CoA dehydrogenase/EHHADH                                    | 261515 | NM_00196<br>6 | 3q27       |
|                           | hydroxyacyl-CoA dehydrogenase/3-ketoacyl-CoA thiolase/enoyl-CoA hydratase, alpha subunit/HADHA | 600890 | NM_00018<br>2 | 2p23       |
|                           | hydroxyacyl-CoA dehydrogenase/3-ketoacyl-CoA thiolase/enoyl-CoA hydratase, beta subunit/HADHB  | 143450 | NM_00018<br>3 | 2p23       |
|                           | acyl-Coenzyme A oxidase 1/ACOX1 (peroxisomal)                                                  | 264470 | NM_00403<br>5 | 17q25      |
|                           | acyl-Coenzyme A oxidase 2, branched chain/ACOX2 (peroxisomal)                                  | 601641 | NM_00350<br>0 | 3p14.3     |

|                                                                |  |                                                                                       |        |           |               |
|----------------------------------------------------------------|--|---------------------------------------------------------------------------------------|--------|-----------|---------------|
|                                                                |  | acyl-Coenzyme A dehydrogenase, C-2 to C-3 short chain precursor/ACADS (mitochondrial) | 201470 | NM_000017 | 12q22-qter    |
|                                                                |  | acyl-Coenzyme A dehydrogenase, C-4 to C-12 straight chain/ACADM (mitochondrial)       | 201450 | NM_000016 | 1p31          |
|                                                                |  | acyl-Coenzyme A dehydrogenase, long chain/ACADL (mitochondrial)                       | 201460 | NM_001608 | 2q34-q35      |
|                                                                |  | hydroxyacyl-Coenzyme A dehydrogenase, type II/HADH2                                   | 602057 | NM_004493 | *****         |
|                                                                |  | enoyl-Coenzyme A hydratase I/ECH1 (peroxisomal)                                       | 600696 | NM_001398 | 19q13         |
| <b>Regulation</b><br>(see also<br><i>parathyroid hormone</i> ) |  | calcitonin/calcitonin gene-related peptide                                            | 114130 | NM_001741 | 1p15.2-p15.1  |
|                                                                |  | calcitonin/calcitonin gene-related peptide                                            | 114160 | X02404    | 1p15.2-p15.2  |
|                                                                |  | calcitonin receptor/CALCR                                                             | 114131 | NM_001742 | 7q21.3        |
|                                                                |  | calcitonin receptor-like/CALCRL                                                       | 114190 | NM_005795 | *****         |
|                                                                |  | stanniocalcin/STC1                                                                    | 601185 | NM_003155 | 8p21-p11.2    |
|                                                                |  | sodium-calcium exchanger (isoform NCX1)                                               | 182305 | AF128524  | 2p23-p22      |
| <b>Uptake</b>                                                  |  | sodium-calcium exchanger (isoform NCX2)                                               | 601901 | *****     | Chr.14        |
|                                                                |  | solute carrier family 12 (sodium/potassium/chloride transporters), member 1/SLC12A1   | 600839 | NM_000338 | 15q15-q21.1   |
| <b>Efflux</b>                                                  |  | regucalcin (senescence marker protein-30)/RGN                                         | 300212 | NM_004683 | Xp11.2-q11.2  |
|                                                                |  | bone gamma-carboxyglutamate (gla) protein (osteocalcin)/BGLAP                         | 112260 | NM_000711 | 1q25-q31      |
|                                                                |  | matrix gamma-carboxyglutamate (gla) protein/MGP/MGLAP                                 | 154870 | NM_000900 | 12p13.1-p12.3 |

**Calcium Metabolism**

|                            |                                          |                                                                                                                 |        |           |            |
|----------------------------|------------------------------------------|-----------------------------------------------------------------------------------------------------------------|--------|-----------|------------|
| <b>Calcium Homeostasis</b> | <b>Calcium Deposition</b>                | gamma-glutamyl carboxylase/GGCX                                                                                 | 137167 | NM_000821 | 2p12       |
|                            |                                          | secreted phosphoprotein 1/SPPI/osteopontin-binding sialoprotein (bone)                                          | 166490 | D14813    | 4q21-q25   |
| <b>Calcium Homeostasis</b> | <b>Bone Growth Factors</b>               | sialoprotein, bone sialoprotein (bone)                                                                          | 147563 | NM_004967 | 4q21-q25   |
|                            |                                          | vitamin D (1,25- dihydroxyvitamin D3) receptor/VDR                                                              | 601769 | NM_000376 | 12q12-q14  |
|                            |                                          | core binding factor alphasubunit/CBFA1/runt-related transcription factor 2/osteoblast-transcription factor 2    | 600211 | AH005498  | 6p21       |
|                            |                                          | osteonectin/ON/secreted protein, acidic, cysteine-rich/SPARC                                                    | 182120 | NM_003118 | 5q31.3-q32 |
|                            |                                          | osteoprotegerin ligand/OPGL/tumor necrosis factor receptor superfamily, member 11a, activator of NFkB/TNFRSF11A | 602642 | NM_003839 | 13q14      |
|                            |                                          | bone morphogenetic protein 1/BMP1                                                                               | 112264 | NM_006132 | 8p21       |
|                            |                                          | bone morphogenetic protein 2 precursor/BMP2                                                                     | 112261 | NM_001200 | 20p12      |
|                            |                                          | bone morphogenetic protein 3 (osteogenic) precursor/BMP3                                                        | 112263 | NM_001201 | 4p14-q21   |
|                            |                                          | bone morphogenetic protein 4/BMP4                                                                               | 112262 | NM_001202 | 14q22-q23  |
|                            |                                          | bone morphogenetic protein 5/BMP5                                                                               | 112265 | *****     | Chr. 6     |
|                            |                                          | bone morphogenetic protein 6/BMP6                                                                               | 112266 | NM_001718 | 6p24-p23   |
|                            |                                          | osteogenic protein 1/OP1/bone morphogenetic protein 7 precursor/BMP7                                            | 112267 | NM_001719 | Chr.20     |
|                            |                                          | osteogenic protein 2/OP2/bone morphogenetic protein 8 precursor/BMP8                                            | 602284 | NM_001720 | 1p35-p32   |
|                            | <b>Bone Growth Factors and Receptors</b> |                                                                                                                 |        |           |            |

|                   |                                                                                                    |        |           |               |
|-------------------|----------------------------------------------------------------------------------------------------|--------|-----------|---------------|
| <b>Receptors</b>  | osteoprotegerin/OPG/tumor necrosis factor receptor superfamily, member 11b/TNFRSF11B               | 602643 | NM_002546 | 8q24          |
|                   | bone morphogenetic protein receptor, type IA/BMPRI A                                               | 601299 | NM_004329 | 10q22.3       |
|                   | bone morphogenetic protein receptor, type IB/BMPRI B                                               | 603248 | NM_001203 | 4q23-q24      |
|                   | bone morphogenetic protein receptor, type II precursor (serine/threonine kinase)/BMPRII            | 600799 | NM_001204 | 2q33-q34      |
|                   | cytochrome P450, subfamily XXVIIB (25-hydroxyvitamin D-1-alpha-hydroxylase), polypeptide 1/CYP27B1 | 264700 | NM_000785 | 12q14         |
| <b>Receptors</b>  | vitamin D (1,25-dihydroxyvitamin D3) receptor/VDR                                                  | 601769 | NM_000376 | 12q12-q14     |
| <b>Signalling</b> | nuclear receptor coactivator 2/GRIP1                                                               | 601993 | NM_006540 | *****         |
|                   | vitamin D3 receptor interacting protein/DRIP80                                                     | *****  | AF105421  | *****         |
|                   | vitamin D3 receptor interacting protein/DRIP92                                                     | *****  | AF106934  | *****         |
|                   | vitamin D3 receptor interacting protein/DRIP130                                                    | *****  | AF105332  | *****         |
| <b>Metabolism</b> | cytochrome P450, subfamily XXIV (vitamin D 24-hydroxylase)/CYP24                                   | 126065 | NM_000782 | 10q13.2-q13.3 |
|                   | serum vitamin D-binding protein/DBP/group-specific component/GC                                    | 139200 | L10641    | 4q12          |
|                   | calbindin 3, (vitamin D-dependent calcium-binding protein)/CALB3                                   | 302020 | NM_004057 | Xp            |

## Vitamin D

| Phosphate Homeostasis | Phosphate Metabolism | Regulation                                                                                           | X-linked hypophosphatemia protein/HYP/phosphate-regulating endopeptidase homolog, X-linked/PHEX/PEX |           |  |  | Xp22.2-p22.1 |
|-----------------------|----------------------|------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------|-----------|--|--|--------------|
|                       |                      |                                                                                                      | 307800                                                                                              | Y10196    |  |  |              |
| Uptake                |                      | alkaline phosphatase, liver/bone/kidney/ALPL                                                         | 171760                                                                                              | NM_000478 |  |  | 1p36.1-p34   |
|                       |                      | solute carrier family 17 (sodium phosphate), member 1/SLC17A1                                        | 182308                                                                                              | NM_005074 |  |  | 6p23-p21.3   |
|                       |                      | solute carrier family 17 (sodium phosphate), member 2/SLC17A2                                        | 182309                                                                                              | NM_003052 |  |  | 5q35         |
|                       |                      | solute carrier family 17 (sodium phosphate), member 4/SLC17A4                                        | 604216                                                                                              | NM_005495 |  |  | 6p22-p21.3   |
|                       |                      | solute carrier family 20 (phosphate transporter), member 1/SLC20A1                                   | 137570                                                                                              | NM_005415 |  |  | 2q11-q14     |
|                       |                      | type II sodium-dependent phosphate transporter 3b/NAPI-3B/solute carrier family 34, member 2/SLC34A2 | 604217                                                                                              | NM_006424 |  |  | *****        |
|                       |                      | interleukin 1 beta/IL1B                                                                              | 147720                                                                                              | AF043335  |  |  | 2q14         |
|                       |                      | interleukin 1 receptor, type I/IL1R1                                                                 | 147810                                                                                              | NM_000877 |  |  | 2q12         |
| Interleukins          |                      | interleukin 1 receptor, type 2/IL1R2                                                                 | 147811                                                                                              | NM_004633 |  |  | 2q12-q22     |
|                       |                      | interleukin 6/IL6                                                                                    | 147620                                                                                              | AF048692  |  |  | 7p21         |
|                       |                      | interleukin 6 receptor/IL6R                                                                          | 147880                                                                                              | NM_000565 |  |  | 1q21         |
|                       |                      | transforming growth factor, beta-1/TGFB1                                                             | 190180                                                                                              | M60315    |  |  | 9q13.1-q13.3 |
| Cytokines             |                      | transforming growth factor, beta-2/TGFB2                                                             | 190220                                                                                              | NM_003238 |  |  | 1q41         |

|                                                        |                                                                                                       |        |           |           |
|--------------------------------------------------------|-------------------------------------------------------------------------------------------------------|--------|-----------|-----------|
| <b>Transforming Growth Factor</b>                      | transforming growth factor, beta-3/TGFB3                                                              | 190230 | NM_003239 | 14q24     |
|                                                        | transforming growth factor, beta receptor I (activin A receptor type II-like kinase, 53kD)/TGFBRI     | 190181 | NM_004612 | 9q33-q34  |
|                                                        | transforming growth factor, beta receptor II (70-80kD)/TGFBRII                                        | 190182 | NM_003242 | 3p22      |
|                                                        | transforming growth factor, beta receptor III (betaglycan, 300kD)/TGFBRIII                            | 600742 | NM_003243 | 1p33-p32  |
| <b>Adhesion Molecules</b>                              | antigen CD51/integrin, alpha-5/beta1 integrin, alpha-5/fibronectin receptor, alpha subunit/FNRA/ITGA5 | 193210 | NM_002210 | 2q31-q32  |
|                                                        | lymphocyte antigen CD11C/integrin, alpha-X/CD11C/ITGAX                                                | 135620 | NM_002205 | 12q11-q13 |
|                                                        | lymphocyte antigen CD11A/integrin, alpha-L/CD11A/ITGAL                                                | 151510 | NM_000887 | 16p11.2   |
|                                                        | matrix metalloproteinase 1 (interstitial collagenase)/MMP1                                            | 153370 | NM_002209 | 16p11.2   |
| <b>Inflammation (additional genes in Inflammation)</b> | matrix metalloproteinase 2 (neutrophil gelatinase)/CLG4/MMP2                                          | 120353 | NM_002421 | 11q22-q23 |
|                                                        | matrix metalloproteinase-like 1/MMPL1                                                                 | *****  | NM_004142 | *****     |
|                                                        | matrix metalloproteinase 3                                                                            | 120360 | AH002654  | 16q13     |
|                                                        | (stromelysin 1, progelatinase)/MMP3                                                                   | 185250 | NM_002422 | 11q23     |
|                                                        | matrix metalloproteinase 8 (neutrophil collagenase)/MMP8                                              | 120355 | NM_002424 | 11q21-q22 |

|           |                                                                                           |        |           |              |
|-----------|-------------------------------------------------------------------------------------------|--------|-----------|--------------|
| Adhesion  | matrix metalloproteinase 9 (gelatinase B, 92kD gelatinase, 92kD type IV collagenase)/MMP9 | 120361 | NM_004994 | 11.2-q13.1   |
|           | matrix metalloproteinase 10 (stromelysin 2)/MMP10                                         | 185260 | NM_002425 | 11q22.3-q23  |
|           | matrix metalloproteinase 11 (stromelysin 3)/MMP11                                         | 185261 | NM_005940 | 22q11.2      |
|           | matrix metalloproteinase 12 (macrophage elastase)/MMP12                                   | 601046 | NM_002426 | 1q22.2-q22.3 |
|           | matrix metalloproteinase 13 (collagenase 3)/MMP13                                         | 600108 | NM_002427 | 11q22.3      |
|           | matrix metalloproteinase 14 (membrane-inserted)/MMP14                                     | 600754 | NM_004995 | 14q11-q12    |
|           | matrix metalloproteinase 15 (membrane-inserted)/MMP15                                     | 602261 | NM_002428 | 16q13-q21    |
|           | matrix metalloproteinase 16 (membrane-inserted)/MMP16                                     | 602262 | NM_005941 | 8q21         |
|           | matrix metalloproteinase 17 (membrane-inserted)/MMP17                                     | 602285 | NM_004141 | 12q24.33     |
|           | matrix metalloproteinase 19/MMP19                                                         | 601807 | NM_002429 | 12q14        |
| Proteases | matrix metalloproteinase 23A/MMP23A                                                       | 603320 | NM_004659 | 1p36.3       |
|           | matrix metalloproteinase 23B/MMP23B                                                       | 603321 | NM_006983 | 1p36.3       |
|           | matrix metalloproteinase 24 (membrane-inserted)/MMP24                                     | *****  | NM_006690 | *****        |

Table 6. Cardiovascular and Renal Gene List



| Class | Pathway          | Function     | Name                                                            | OMIM   | GID       | Locus         |
|-------|------------------|--------------|-----------------------------------------------------------------|--------|-----------|---------------|
|       | Dopamine Pathway | Biosynthesis | aromatic L-Amino Acid                                           | 107930 | AH005280  | 7p11          |
|       |                  |              | Decarboxylase/AADC/dopa decarboxylase                           |        |           |               |
|       |                  | Receptors    | tyrosine hydroxylase/TH                                         | 191290 | NM_000360 | 11p15.5       |
|       |                  |              | dopamine receptor D1/DRD1                                       | 126449 | NM_000794 | 5q35.1        |
|       |                  |              | dopamine Receptor D2/DRD2                                       | 126450 | NM_000795 | 11q23         |
|       |                  |              | dopamine Receptor D3/DRD3                                       | 126451 | NM_000796 | 3q13.3        |
|       |                  |              | dopamine receptor D4/DRD4                                       | 126452 | NM_000797 | 11p15.5       |
|       |                  |              | dopamine receptor D5/DRD5                                       | 126453 | NM_000798 | 4p16.1-p15.3  |
|       |                  | Reuptake     | solute carrier family 6 member 3/SLC6A3 (dopamine)              | 126455 | NM_001044 | 5p15.3        |
|       |                  |              | dopamine beta-hydroxylase (dopamine beta-monooxygenase)/DBH     | 223360 | NM_000787 | 9q34          |
|       | Dopamine Pathway | Catabolism   | catechol-O-methyltransferase/COMT                               | 116790 | NM_000754 | 22q11.2       |
|       |                  |              | monoamine oxidase A, nuclear gene encoding mitochondrial        | 309850 | NM_000240 | Xp11.23       |
|       |                  |              | monoamine oxidase B, nuclear gene encoding mitochondrial        | 309860 | NM_000898 | Xp11.23       |
|       |                  |              | phenol-preferring sulfotransferase, family 1A, member 1/SULT1A1 | 171150 | NM_001055 | 16p12.1-p11.2 |
|       |                  |              | phenol-preferring sulfotransferase, family 1A, member 2/SULT1A2 | 601292 | NM_001054 | 16p12.1-p11.2 |
|       |                  |              | phenol-preferring sulfotransferase, family 1A, member 3/SULT1A3 | 600641 | L19956    | 16p11.2       |
|       |                  | Biosynthesis | dopamine beta-hydroxylase (dopamine beta-monooxygenase)/DBH     | 223360 | NM_000787 | 9q34          |
|       |                  |              | phenylethanolamine-N-methyltransferase/PNMT                     | 171190 | NM_002686 | 17q21-q22     |

|                   | tyrosine hydroxylase/TH                                                                | 191290 | NM_000360 | 11p15.5    |
|-------------------|----------------------------------------------------------------------------------------|--------|-----------|------------|
| <b>Receptors</b>  | adrenergic receptor alpha-1A<br>/ADRA1A                                                | 104219 | NM_000678 | Chr.20     |
|                   | adrenergic receptor alpha-1B                                                           | 104220 | NM_000679 | 5q33       |
|                   | adrenergic receptor alpha-1C<br>/ADRA1C                                                | 104221 | NM_000680 | 8p21       |
|                   | adrenergic receptor alpha-1D<br>/ADRA1D                                                | 104222 | M76446    | 20p13      |
|                   | adrenergic receptor alpha-2A<br>(platelet)/ADRA2A                                      | 104210 | NM_000681 | 10q24-q26  |
|                   | adrenergic receptor alpha-2B (hepatic,<br>renal)/ADRA2B                                | 104260 | NM_000682 | Chr.2      |
|                   | adrenergic receptor alpha-2C<br>(renal)/ADRA2C                                         | 104250 | NM_000683 | 4q16.1     |
|                   | adrenergic receptor beta-1/ADRB1                                                       | 109630 | NM_000684 | 10q24-q26  |
|                   | adrenergic receptor beta-2/ADRB2                                                       | 109690 | NM_000024 | 5q32-q34   |
|                   | adrenergic receptor beta-3/ADRB3                                                       | 109691 | NM_000025 | 8p12-p11.2 |
| <b>Signalling</b> | beta-adrenergic receptor kinase<br>1/ADRBK1/BARK                                       | 109635 | NM_001619 | 11cen-q13  |
|                   | beta-adrenergic receptor kinase<br>2/ADRBK2                                            | 109636 | X69117    | 22q11      |
|                   | guanine nucleotide binding protein (G<br>protein), beta polypeptide 2-like<br>1/GNB2L1 | 109760 | NM_006098 | 5q11.2-q13 |
|                   | arrestin, beta 1/ARRB1                                                                 | 107940 | NM_004041 | 11q13      |
|                   | vesicular amine transporter 2 / VAT2                                                   | 193001 | L09118    | 10q25      |
| <b>Reuptake</b>   | vesicular amine transporter 1/ VAT1                                                    | 193002 | *****     | 8p21.3     |
|                   | Solute carrier family 6 , member<br>5/SLC6A2/NAT1/NET1                                 | 163970 | NM_001043 | 16q12.2    |

**Epinephrine  
and Nor-  
epinephrine  
Pathway**

|              |                                                                                        |        |           |               |
|--------------|----------------------------------------------------------------------------------------|--------|-----------|---------------|
| Catabolism   | monamine oxidase A, nuclear gene<br>encoding mitochondrial<br>monoamine oxidase A      | 309850 | NM_000240 | Xp11.23       |
|              | monamine oxidase B, nuclear gene<br>encoding mitochondrial<br>monoamine oxidase B      | 309860 | NM_000898 | Xp11.23       |
|              | catechol-O-methyltransferase/COMT                                                      | 116790 | NM_000754 | 22q11.2       |
| Biosynthesis | choline acetyltransferase/CHAT                                                         | 118490 | NM_003055 | 10q11.2       |
|              | carnitine acetyltransferase/CRAT                                                       | 600184 | NM_004003 | 9q34.1        |
|              | apolipoprotein E                                                                       | 107741 | NM_000041 | 19q13.2       |
|              | cholinergic receptor, muscarinic<br>1/CHRM1                                            | 118510 | NM_000738 | 11q13         |
|              | cholinergic receptor, muscarinic<br>1/CHRM2                                            | 118493 | NM_000739 | 7q35-q36      |
|              | cholinergic receptor, muscarinic<br>1/CHRM3                                            | 118494 | U29589    | 1q41-q44      |
|              | cholinergic receptor, muscarinic<br>1/CHRM4                                            | 118495 | NM_000741 | 11p12-p11.2   |
|              | cholinergic receptor, muscarinic<br>1/CHRM5                                            | 118496 | AF026263  | 15q26         |
|              | cholinergic receptor, nicotinic, alpha<br>polypeptide 1 (muscle)<br>precursor/CHRNA1   | 100690 | NM_000079 | 2q24-q32      |
|              | cholinergic receptor, nicotinic, alpha<br>polypeptide 2 (neuronal)/CHRNA2              | 118502 | NM_000742 | Chr.8         |
|              | cholinergic receptor, nicotinic, alpha<br>polypeptide 3 (neuronal)<br>precursor/CHRNA3 | 118503 | NM_000743 | 15q24         |
|              | cholinergic receptor, nicotinic, alpha<br>polypeptide 4 (neuronal)<br>precursor/CHRNA4 | 118504 | NM_000744 | 20q13.2-q13.3 |
|              |                                                                                        |        |           |               |
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|------------------------------|-------------------|----------------------------------------------------------------------------------|--------|-----------|--------------|
| <b>Acetylcholine Pathway</b> | <b>Receptors</b>  | cholinergic receptor, nicotinic, alpha polypeptide 5 (neuronal) precursor/CHRNA5 | 118505 | NM_000745 | 15q24        |
|                              |                   | cholinergic receptor, nicotinic, alpha polypeptide 6 (neuronal) precursor/CHRNA6 | *****  | NM_004198 | *****        |
|                              |                   | cholinergic receptor, nicotinic, alpha polypeptide 7 (neuronal) precursor/CHRNA7 | 118511 | NM_000746 | 15q14        |
|                              |                   | cholinergic receptor, nicotinic, beta polypeptide 1 (muscle)/CHRNA1              | 100710 | NM_000747 | 17p12-p11    |
|                              |                   | cholinergic receptor, nicotinic, beta polypeptide 2 (neuronal)/CHRNA2            | 118507 | NM_000748 | 1p21         |
|                              |                   | cholinergic receptor, nicotinic, beta polypeptide 3/CHRNA3                       | 118508 | NM_000749 | 8p11.2       |
|                              |                   | cholinergic receptor, nicotinic, beta polypeptide 4/CHRNA4                       | 118509 | NM_000750 | 15q24        |
|                              |                   | cholinergic receptor, nicotinic, epsilon polypeptide/CHRNAE                      | 100725 | NM_000080 | Chr.17       |
|                              |                   | cholinergic receptor, nicotinic, delta polypeptide/CHRNA                         | 100720 | NM_000751 | 2q33-q34     |
|                              |                   | cholinergic receptor, nicotinic, gamma polypeptide/CHRNA                         | 100730 | NM_005199 | 2q33-q34     |
|                              | <b>Reuptake</b>   | solute carrier family 18 (vesicular acetylcholine), member 3/SLC18A3             | 600336 | NM_003055 | 10q11.2      |
|                              | <b>Catabolism</b> | acetylcholinesterase (YT blood group) precursor/ACHE                             | 100740 | NM_000665 | 7q22         |
|                              |                   | butyrylcholinesterase 1/serum cholinesterase 1/BCHE1                             | 177400 | NM_000055 | 3q26.1-q26.2 |

|                     |                                                                                                                   |        |           |             |
|---------------------|-------------------------------------------------------------------------------------------------------------------|--------|-----------|-------------|
|                     | butyrylcholinesterase 2/serum cholinesterase 2/BCHE2                                                              | 177500 | *****     | 2q33-q35    |
|                     | aromatic L-Amino Acid Decarboxylase/AADC                                                                          | 107930 | AH005280  | 7p11        |
|                     | tryptophan hydroxylase (tryptophan 5-monooxygenase)/TPH                                                           | 191060 | NM_004179 | 11p15.3-p14 |
|                     | 14-3-3 protein tyrosine 3-monooxygenase/tryptophan 5-monooxygenase activation protein, eta polypeptide/YWHAH      | 113508 | NM_003405 | 22q12       |
|                     | 14-3-3 protein tyrosine 3-monooxygenase/tryptophan 5-monooxygenase activation protein, epsilon polypeptide/YWHA E | *****  | NM_006761 | *****       |
|                     | 14-3-3 protein tyrosine 3-monooxygenase/tryptophan 5-monooxygenase activation protein, zeta polypeptide/YWHA Z    | 601288 | NM_003406 | 2p25.1      |
|                     | 14-3-3 protein tyrosine 3-monooxygenase/tryptophan 5-monooxygenase activation protein, beta polypeptide/YWHA B    | 601289 | NM_003404 | 20q13.1     |
|                     | 14-3-3 protein tyrosine 3-monooxygenase/tryptophan 5-monooxygenase activation protein, theta polypeptide/YWHA Q   | *****  | NM_006826 | *****       |
|                     | G protein-coupled 5-hydroxytryptamine (serotonin)                                                                 | 109760 | NM_000524 | 5q11.2-q13  |
| <b>Biosynthesis</b> |                                                                                                                   |        |           |             |

**Serotonin  
Pathway**

**Receptors**

|                                                   |        |           |              |
|---------------------------------------------------|--------|-----------|--------------|
| G protein-coupled 5-hydroxytryptamine (serotonin) | 182131 | NM_000863 | 6q13         |
| G protein-coupled 5-hydroxytryptamine (serotonin) | 312861 | U49516    | Xq24         |
| G protein-coupled 5-hydroxytryptamine (serotonin) | 182133 | NM_000864 | 1p36.3-p34.3 |
| G protein-coupled 5-hydroxytryptamine (serotonin) | 182132 | NM_000865 | 6q14-q15     |
| G protein-coupled 5-hydroxytryptamine (serotonin) | 182134 | L05597    | 3p12         |
| G protein-coupled 5-hydroxytryptamine (serotonin) | 182135 | D87030    | 13q14-q21    |
| G protein-coupled 5-hydroxytryptamine (serotonin) | 601122 | NM_000867 | 2q36.3-q37.1 |
| G protein-coupled 5-hydroxytryptamine (serotonin) | 312861 | NM_000868 | Xq24         |
| gated ion channel 5-hydroxytryptamine (serotonin) | 182139 | NM_000869 | 1q23.1-q23.2 |
| gated ion channel 5-hydroxytryptamine (serotonin) | *****  | NM_006028 | *****        |
| G protein-coupled 5-hydroxytryptamine (serotonin) | 602164 | Y08756    | 5q31-q33     |
| G protein-coupled 5-hydroxytryptamine (serotonin) | 601305 | X81411    | 7q36.1       |
| G protein-coupled 5-hydroxytryptamine (serotonin) | 601109 | NM_000871 | 1p36-p35     |
| G protein-coupled 5-hydroxytryptamine (serotonin) | 182137 | L21195    | 10q21-q24    |

|                            |              |                                                                                          |        |           |               |
|----------------------------|--------------|------------------------------------------------------------------------------------------|--------|-----------|---------------|
| Neuro-<br>and<br>Adenosine | Reuptake     | solute carrier family 6<br>(neurotransmitter transporter,<br>serotonin), member 4/SLC6A4 | 182138 | NM_001045 | 17q11.1-q12   |
|                            | Catabolism   | monoamine oxidase A, nuclear gene<br>encoding mitochondrial                              | 309850 | NM_000240 | Xp11.23       |
|                            |              | monoamine oxidase B, nuclear gene<br>encoding mitochondrial                              | 309860 | M69177    | Xp11.23       |
|                            |              | serotonin N-Acetyltransferase/SNAT                                                       | 600950 | U40347    | 17q25         |
|                            | Biosynthesis | tryptophan 2,3-dioxygenase/TDO2                                                          | 191070 | NM_005651 | 4q31-q32      |
|                            |              | adenylosuccinate lyase/ADSL                                                              | 103050 | NM_000026 | 22q13.1       |
|                            |              | adenylosuccinate synthetase/ADSS                                                         | 103060 | NM_001126 | 1cen-q12      |
|                            |              | adenosine A1 receptor (G-protein<br>coupled)/ADORA1                                      | 102775 | NM_000674 | 1q32.1        |
|                            |              | adenosine A2a receptor (G-protein<br>coupled)/ADORA2A                                    | 102776 | NM_000675 | 22q11.2       |
|                            |              | adenosine A2b receptor (G-protein<br>coupled)/ADORA2B                                    | 600446 | NM_000676 | 17p12-p11.2   |
|                            |              | adenosine A3 receptor (G-protein<br>coupled)/ADORA3                                      | 600445 | NM_000677 | 1p21-p13      |
|                            |              | adenosine A2 receptor-<br>like/ADORA2L1                                                  | 102777 | *****     | 10q25.3-q26.1 |
|                            |              | purinergic receptor P2X, ligand-gated<br>ion channel, 1/P2RX1                            | 600845 | NM_002558 | *****         |
|                            |              | purinergic receptor P2X, ligand-gated<br>ion channel, 3/P2RX3                            | 600843 | NM_002559 | 11q12         |
|                            | Receptors    | purinergic receptor P2X, ligand-gated<br>ion channel, 4/P2RX4                            | 600846 | NM_002560 | 12q24.32      |
|                            |              | purinergic receptor P2X, ligand-gated<br>ion channel, 5/P2RX5                            | 602836 | NM_002561 | *****         |

| Enzyme                | Pathway | Control of Heart Rate, Vascular Tone, and Renal Function                    |        |            |              |
|-----------------------|---------|-----------------------------------------------------------------------------|--------|------------|--------------|
|                       |         | Enzyme                                                                      | Gene   | Chromosome |              |
|                       |         | purinergic receptor P2X, ligand-gated ion channel, 7/P2RX7                  | 602566 | NM_002562  | 12q24        |
|                       |         | purinergic receptor P2Y (G-protein coupled) 1/P2RY1                         | 601167 | NM_002563  | 3q25         |
|                       |         | purinergic receptor P2Y (G-protein coupled) 2/P2RY2                         | 600041 | U07225     | 1q13.5-q14.1 |
|                       |         | purinergic receptor P2Y (G-protein coupled) 4/P2RY4                         | 300038 | NM_002565  | Xq13         |
|                       |         | purinergic receptor P2Y (G-protein coupled) 6/P2RY6                         | 602451 | NM_004154  | 11q13.5      |
|                       |         | leukotriene B4 receptor/purinergic receptor P2Y (G-protein coupled) 7/P2RY7 | 601531 | NM_000752  | 14q11.2-q12  |
|                       |         | purinergic receptor P2Y (G-protein coupled) 11/P2RY11                       | 602697 | NM_002566  | *****        |
|                       |         | Solute carrier family 29 (nucleosides), member 1/SLC29A1/ENT1               | 602193 | NM_004955  | 6p21.2-p21.1 |
|                       |         | Solute carrier family 29 (nucleosides), member 2/SLC29A2/ENT2               | 602110 | X86681     | 11q13        |
|                       |         | adenosine deaminase                                                         | 102700 | NM_000022  | 20q13.11     |
|                       |         | Histidine Decarboxylase                                                     | 142704 | M60445     | 15q21-q22    |
|                       |         | histamine H1 receptor/HRH1                                                  | 600167 | NM_000861  | 3p21-p14     |
|                       |         | histamine H2 receptor/HRH2                                                  | 142703 | AB023486   | *****        |
| Histaminergic Pathway |         | histamine H3 receptor/HRH3                                                  | *****  | NM_007232  | *****        |
|                       |         | Histamine N-                                                                | *****  | NM_006895  | chr. 2       |
|                       |         | Amine oxidase (copper-containing) 2/AOC2                                    | 602268 | D88213     | 17q21        |



|                                                  |                                   |                                                               |        |           |              |
|--------------------------------------------------|-----------------------------------|---------------------------------------------------------------|--------|-----------|--------------|
|                                                  |                                   | Amine oxidase (copper-containing)<br>3/AOC3                   | 603735 | AF054985  | 17q21        |
| Nitric Oxide<br>Pathway                          | Biosynthesis                      | nitric oxide synthetase 1/NOS1                                | 163731 | AH001515  | 2q24.2-q24.3 |
|                                                  |                                   | nitric oxide synthetase 2A/NOS2A                              | 163730 | X85766    | 17cen-q11.2  |
|                                                  |                                   | macrophage nitric oxide synthetase<br>2B/NOS2B                | 600719 | AH006623  | 17p13.1-q25  |
|                                                  |                                   | macrophage nitric oxide synthetase<br>2C/NOS2C                | 600720 | 600720    | 17p13.1-q25  |
|                                                  |                                   | nitric oxide synthetase 3/NOS3                                | 163729 | AH001515  | 7q36         |
|                                                  |                                   | chondrocyte nitric oxide synthetase<br>3/NOS4                 | 163728 | X73029    | *****        |
|                                                  |                                   | arginase/ARG1                                                 | 207800 | NM_000045 | *****        |
|                                                  |                                   | arginase/ARG2                                                 | 107830 | NM_001172 | 4q24.1-q24.2 |
|                                                  |                                   | guanylate cyclase 1, soluble, beta 2/GU                       | 603695 | AF038499  | 13q14.3      |
|                                                  |                                   | guanylate cyclase 1, soluble, beta 3/GU                       | 139397 | NM_000857 | 4q32         |
| General<br>Metabolism<br>for Peptide<br>Hormones | Receptors                         | guanylate cyclase 1, soluble, alpha 3/G                       | 139396 | NM_000856 | 4q32         |
|                                                  |                                   | guanylate cyclase 1, soluble, alpha 2/G                       | 601244 | NM_000855 | 11q21-q22    |
|                                                  |                                   | membrane<br>metalloendopeptidase/MME/neutral<br>endopeptidase | 120520 | NM_000902 | 3q21-q27     |
|                                                  |                                   | calpain, large polypeptide L3/CAPN3                           | 114240 | NM_000070 | 5q15.1-q21.1 |
|                                                  |                                   | leucyl/cystinyl                                               | 151300 | NM_005575 | *****        |
|                                                  |                                   | carboxypeptidase N polypeptide<br>1/CPN1                      | 603103 | NM_001308 | chr. 10      |
|                                                  |                                   | carboxypeptidase N polypeptide<br>2/regulatory subunit/CPN2   | 603104 | J05158    | 8p23-p22     |
|                                                  |                                   | meprin alpha subunit/MEP1A                                    | 600388 | NM_005925 | 6p21.2-p21.1 |
|                                                  |                                   | meprin beta subunit/MEP1B                                     | 600389 | NM_005925 | 8q12.2-q12.3 |
|                                                  |                                   | prolyl endopeptidase/PREP                                     | 600400 | NM_002726 | 6q22         |
| General<br>Metabolism<br>for Peptide<br>Hormones | Biosynthesis<br>and<br>Catabolism |                                                               |        |           |              |
|                                                  |                                   |                                                               |        |           |              |
|                                                  |                                   |                                                               |        |           |              |
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|------------------------------|---------------------|-----------------------------------------------------------------------|--------|-----------|--------------|
|                              |                     | neuroendocrine convertase 1/NEC1                                      | 162150 | D73407    | 5q14-q21     |
|                              |                     | peptidylglycine alpha-amidating monooxygenase /PAM/NEC2               | 170270 | NM_000919 | 5q14-q21     |
|                              |                     | paired basic amino acid cleaving enzyme/PACE/FUR                      | 136950 | X04329    | 15q25-q26    |
|                              | <b>Biosynthesis</b> | Cholecystokinin/CCK                                                   | 118440 | NM_000729 | 3pter-p21    |
| <b>Cholecystokinin (CCK)</b> | <b>Receptors</b>    | Cholecystokinin A receptor/CCKAR                                      | 118444 | NM_000730 | 4p15.2-p15.1 |
|                              |                     | Cholecystokinin B receptor/CCKBR                                      | 118445 | NM_000731 | 1p15.5-p15.4 |
|                              | <b>Biosynthesis</b> | Neuropeptide Y/NPY                                                    | 162640 | NM_000905 | 7p15.1       |
|                              |                     | Neuropeptide Y receptor Y1/NPY1R                                      | 162641 | NM_000909 | 4q31.3-q32   |
|                              |                     | Neuropeptide Y receptor Y2/NPY2R                                      | 162642 | NM_000910 | 4q31         |
|                              | <b>Receptors</b>    | Neuropeptide Y receptor Y3/chemokine receptor                         | 162643 | X71635    | 2q21         |
| <b>Neuropeptide Y (NPY)</b>  |                     | Neuropeptide Y receptor Y5/NPY5R                                      | 602001 | NM_006174 | 4q31-q32     |
|                              |                     | Neuropeptide Y receptor Y6/NPY6R                                      | 601770 | NM_006173 | 5q31         |
|                              | <b>Biosynthesis</b> | kininogen/KNG                                                         | 228960 | *****     | 3q27         |
|                              |                     | kallikrein 1/KLK1                                                     | 147910 | AH002853  | 9q13.2-q13.4 |
|                              |                     | bradykinin receptor B1/BDKRBI G                                       |        |           |              |
|                              | <b>Receptor</b>     | protein-coupled                                                       | 600337 | NM_000710 | 4q32.1-q32.2 |
|                              |                     | bradykinin receptor B2/BDKRBB2 G                                      |        |           |              |
|                              |                     | protein-coupled                                                       | 113503 | NM_000623 | 4q32.1-q32.2 |
| <b>Bradykinin</b>            | <b>Catabolism</b>   | X-prolyl aminopeptidase (aminopeptidase P) 2, membrane-bound/XPNIPEP2 | 300145 | NM_003399 | Xq25         |
|                              |                     | carboxypeptidase N, polypeptide 1, 50kD/CPN1                          | 603103 | NM_001308 | Chr.10       |
|                              |                     | carboxypeptidase N, polypeptide 2, 83kD/CPN2                          | 603104 | *****     | 8p23-p22     |

| Adrenomedullin | Biosynthesis | adrenomedullin/ADM                                                                                    | 103275 | NM_001124 | 11p15.4   |
|----------------|--------------|-------------------------------------------------------------------------------------------------------|--------|-----------|-----------|
| Angiotensin    | Biosynthesis | angiotensinogen/angiotensin I/AGT                                                                     | 106150 | NM_000029 | 1q42-q43  |
|                |              | renin/REN                                                                                             | 179820 | NM_000537 | 1q32      |
|                |              | renin-binding protein/RENBP                                                                           | 312420 | NM_002910 | Xq28      |
|                |              | membrane metalloendopeptidase/MME/neutral endopeptidase                                               | 120520 | NM_000902 | 3q21-q27  |
|                |              | thimet oligopeptidase 1/THOP1                                                                         | 601117 | NM_003249 | 19p13.3   |
|                |              | chymase 1, mast cell/CMA1                                                                             | 118938 | NM_001836 | 14q11.2   |
|                |              | angiotensin converting enzyme/dipeptidyl                                                              | 106180 | NM_000789 | 17q23     |
|                |              | angiotensin receptor 1/AGTR1                                                                          | 106165 | NM_000685 | 3q21-q25  |
|                |              | angiotensin receptor 1B/AGTR1B                                                                        | 600015 | NM_004835 | *****     |
|                |              | angiotensin receptor-like 1/AGTRL1                                                                    | 600052 | NM_005161 | 11q12     |
| Vasopressin    | Receptors    | angiotensin receptor-like 2/AGTRL2                                                                    | 601256 | NM_005162 | *****     |
|                |              | angiotensin receptor 2/AGTR2                                                                          | 300034 | NM_000686 | Xq22-q23  |
|                |              | X-prolyl aminopeptidase (aminopeptidase P) 2, membrane-bound/XPNPEP2                                  | 300145 | NM_003399 | Xq25      |
|                |              | prolylcarboxypeptidase/PRCP                                                                           | 176785 | NM_005040 | 11q14     |
|                |              | arginine vasopressin (neurophysin II, antidiuretic hormone, diabetes insipidus, neurohypophyseal)/AVP | 192340 | NM_000490 | 20p13     |
|                |              | arginine vasopressin receptor 1A/AVPR1A                                                               | 600821 | NM_000706 | 12q14-q15 |
|                |              | arginine vasopressin receptor 1B/AVPR1B                                                               | 600264 | NM_000707 | 1q32      |
|                |              |                                                                                                       |        |           |           |
|                |              |                                                                                                       |        |           |           |
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|--|----------------------------------------------|-----------------------------------------------------------------------------------------------------|--------|-----------|-----------|
|  |                                              | arginine vasopressin receptor 2<br>(nephrogenic diabetes)                                           | 304800 | NM_000054 | Xq28      |
|  | <b>Catabolism</b>                            | leucyl/cystinyl                                                                                     | 151300 | NM_005575 | *****     |
|  | <b>Biosynthesis</b>                          | prepro-vasoactive intestinal<br>adenylate-cyclase activating<br>polypeptide 1/ADCYAP1               | 192320 | AH003029  | 6q26-q27  |
|  | <b>Vasoactive<br/>Intestinal<br/>Peptide</b> | vasoactive intestinal peptide receptor<br>1/VIPR1                                                   | 102980 | NM_001117 | 18p11     |
|  |                                              | vasoactive intestinal peptide receptor<br>2/VIPR2                                                   | 192321 | NM_004624 | 3p22      |
|  |                                              | adenylate cyclase activating<br>polypeptide 1 (pituitary) receptor type<br>1/ADCYAP1R1              | 601970 | NM_003382 | 7q36.3    |
|  |                                              | atrial natriuretic peptide precursor<br>A/NPPA                                                      | 102981 | NM_001118 | 7p14      |
|  |                                              | natriuretic peptide precursor B/NPPB                                                                | 108780 | X01471    | 1p36.2    |
|  | <b>Biosynthesis</b>                          | atrial natriuretic peptide precursor<br>C/NPPC                                                      | 600295 | NM_002521 | 1p36.2    |
|  | <b>Natriuretic<br/>Peptide</b>               | natriuretic peptide receptor<br>A/guanylate cyclase A (atrionatriuretic<br>peptide receptor C)/NPR1 | 600296 | D28874    | 2q24-qter |
|  |                                              | natriuretic peptide receptor<br>B, isoform<br>a/NPR2                                                | 108960 | NM_000906 | 1q21-q22  |
|  |                                              | natriuretic peptide receptor<br>C/guanylate cyclase C (atrionatriuretic<br>peptide receptor C)/NPR3 | 108961 | NM_000907 | 9p21-p12  |
|  |                                              | cytochrome P450, subfamily XIB,<br>polypeptide 2 (steroid 11-b-<br>hydroxylase)/CYP11B2             | 108962 | NM_000908 | 5p14-p12  |
|  |                                              |                                                                                                     | 124080 | NM_000498 | 8q21      |
|  | <b>Synthesis<br/>(additional)</b>            |                                                                                                     |        |           |           |

|                                                                      |                                                   |                                                                                     |        |           |           |
|----------------------------------------------------------------------|---------------------------------------------------|-------------------------------------------------------------------------------------|--------|-----------|-----------|
| <b>Mineralocorticosteroids</b><br>(aldosterone, deoxycorticosterone) | <i>genes in steroid hormone metabolism below)</i> | sodium channel, nonvoltage-gated 1 alpha/SCNN1A                                     | 600228 | NM_001038 | 12p13     |
|                                                                      |                                                   | sodium channel, nonvoltage-gated 1, beta (Liddle syndrome)/SCNN1B                   | 600760 | NM_000336 | 16p13-p12 |
|                                                                      |                                                   | sodium channel, nonvoltage-gated 1, gamma/SCNN1G                                    | 600761 | NM_001039 | 16p13-p12 |
|                                                                      |                                                   | mineralocorticoid receptor/MCR/nuclear receptor subfamily 3, group C, member        | 600983 | NM_000901 | 4q31.1    |
| <b>Receptor and Coactivators</b>                                     |                                                   | nuclear receptor coactivator 2/GRIP1                                                | 601993 | NM_006540 | *****     |
|                                                                      |                                                   | oxysterol binding protein/OSBP                                                      | 167040 | NM_002556 | 11q12-q13 |
|                                                                      |                                                   | sterol regulatory element binding transcription factor 1/SREBF1                     | 184756 | NM_004176 | 17p11.2   |
|                                                                      |                                                   | sterol regulatory element binding transcription factor 2/SREBF2                     | 600481 | NM_004599 | 22q13     |
|                                                                      |                                                   | steroid receptor coactivator 1/SRC1                                                 | 602691 | NM_003743 | 2p23      |
|                                                                      |                                                   | steroid receptor RNA activator/SRA                                                  | 603819 | AF092038  | Chr. 5    |
| <b>Estrogens</b>                                                     | <b>Synthesis</b>                                  | cytochrome P450, subfamily XIX (androgen aromatase)/CYP19                           | 107910 | NM_000103 | 15q21.1   |
|                                                                      | <b>Receptors</b>                                  | estrogen receptor 1/ESR1                                                            | 133430 | NM_000125 | 6q25.1    |
|                                                                      |                                                   | estrogen receptor 2/ESR2                                                            | 601663 | X99101    | 14q       |
|                                                                      |                                                   | estrogen-related receptor                                                           | 601998 | NM_004451 | 11q12     |
| <b>Catabolism</b>                                                    |                                                   | estrogen-related receptor beta/ESRRB                                                | 602167 | NM_004452 | 14q24.3   |
|                                                                      |                                                   | estrogen-prefering                                                                  | 600043 | NM_005420 | 4q13.1    |
|                                                                      |                                                   | hydroxy-delta-5-steroid dehydrogenase, 3 beta- and steroid delta-isomerase 1/HSD3B1 | 109715 | NM_000862 | 1p13.1    |
|                                                                      | <b>Synthesis</b>                                  |                                                                                     |        |           |           |

|                                      |                      |                                                                                                             |        |           |            |
|--------------------------------------|----------------------|-------------------------------------------------------------------------------------------------------------|--------|-----------|------------|
| <b>Progestins</b>                    | <b>Synthesis</b>     | hydroxy-delta-5-steroid dehydrogenase, 3 beta- and steroid delta-isomerase 2/HSD3B2                         | 201810 | NM_000198 | 1p13.1     |
|                                      | <b>Receptors</b>     | progesterone receptor/PGR                                                                                   | 264080 | NM_000926 | 11q22      |
| <b>Androgens</b>                     | <b>Synthesis</b>     | heat shock 90-kD protein 1, alpha subunit/HSPCA                                                             | 140571 | *****     | 1q21.2-q22 |
|                                      |                      | heat shock 90-kD protein 1, beta subunit/HSPCB                                                              | 140572 | J04988    | 6p12       |
|                                      |                      | FK506-binding protein 5/FKBP5                                                                               | 602623 | NM_004117 | *****      |
|                                      |                      | steroid-5-alpha-reductase, alpha polypeptide 1 (3-oxo-5 alpha-steroid delta 4-dehydrogenase alpha 1)/SRD5A1 | 184753 | NM_001047 | 5p15       |
|                                      |                      | hydroxysteroid (17-beta) dehydrogenase 3/HSD17B3                                                            | 264300 | NM_000197 | 9q22       |
|                                      | <b>Receptor</b>      | cytochrome P450, subfamily XIA (cholesterol side chain cleavage)/CYP11A                                     | 118485 | NM_000781 | 15q23-q24  |
|                                      |                      | steroid 5-alpha-reductase 2/SRD5A2                                                                          | 264600 | NM_000348 | 2p23       |
|                                      |                      | androgen receptor (dihydrotestosterone receptor)/AR                                                         | 313700 | NM_000044 | Xq11-q12   |
|                                      |                      | UDP glycosyltransferase 2 family, polypeptide B17/UGT2B17                                                   | 601903 | NM_001077 | 4q13       |
|                                      |                      | nuclear receptor coactivator 2/GRIP1                                                                        | 601993 | NM_006540 | *****      |
| <b>Mediators of Steroid Response</b> | <b>Catabolism</b>    | oxysterol binding protein/OSBP                                                                              | 167040 | NM_002556 | 11q12-q13  |
|                                      | <b>Transcription</b> | sterol regulatory element binding transcription factor 1/SREBF1                                             | 184756 | NM_004176 | 17p11.2    |

|                                    |              |                                                                                                               |        |           |               |
|------------------------------------|--------------|---------------------------------------------------------------------------------------------------------------|--------|-----------|---------------|
| (common to the steroid hormones)   | n Factors    | sterol regulatory element binding transcription factor 2/SREBF2                                               | 600481 | NM_004599 | 22q13         |
|                                    |              | steroid receptor coactivator 1/SRC1                                                                           | 602691 | NM_003743 | 2p23          |
|                                    |              | steroid receptor RNA activator/SRA                                                                            | 603819 | AF092038  | Chr. 5        |
|                                    |              | vascular endothelial growth factor/VEGFA                                                                      | 192240 | NM_003376 | 6p12          |
| Vascular Endothelial Growth Factor | Biosynthesis | vascular endothelial growth factor/VEGFB                                                                      | 601398 | NM_003377 | 11q13         |
|                                    |              | vascular endothelial growth factor/VEGFC                                                                      | 601528 | NM_005429 | *****         |
|                                    |              | kinase insert domain receptor/KDR/FLK1/VEGF receptor/VEGFR                                                    | 191306 | AF063657  | 4q12          |
|                                    |              | fms-related tyrosine kinase 1 (vascular endothelial growth factor/vascular permeability factor receptor)/FLT1 | 165070 | NM_002019 | 13q12         |
| Growth Hormone                     | Biosynthesis | growth hormone/GHI                                                                                            | 139250 | NM_000515 | 17q22-q24     |
|                                    | Receptors    | growth hormone receptor/GHR                                                                                   | 600946 | NM_000163 | 5p13-p12      |
| Endothelin                         | Biosynthesis | endothelin 1/EDN1                                                                                             | 131240 | NM_001955 | 6p24-p23      |
|                                    |              | endothelin 2/EDN2                                                                                             | 131241 | NM_001956 | 1p34          |
|                                    |              | endothelin 3/EDN3                                                                                             | 131242 | NM_000114 | 20q13.2-q13.3 |
|                                    |              | endothelin converting enzyme 1/ECE1                                                                           | 600423 | NM_001397 | 1p36.1        |
|                                    | Receptors    | endothelin A receptor isoform delta 3/EDNRA                                                                   | 131243 | AF014826  | Chr.4         |
|                                    |              | endothelin receptor type B/EDNRB                                                                              | 131244 | NM_000115 | 13q22         |
|                                    |              | protein kinase C beta/PRKCB                                                                                   | 176970 | X06318    | 16p11.2       |
|                                    |              | transforming growth factor, beta-1/TGFB1                                                                      | 190180 | M60315    | 9q13.1-q13.2  |

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| <b>Transforming Growth Factor Beta</b> | <b>Biosynthesis</b> | transforming growth factor, beta-2/TGFB2                                                          | 190220 | NM_003238 | 1q41        |
|                                        |                     | transforming growth factor, beta-3/TGFB3                                                          | 190230 | NM_003239 | 14q24       |
| <b>Receptors</b>                       |                     | transforming growth factor, beta receptor I (activin A receptor type II-like kinase, 53kD)/TGFBRI | 190181 | NM_004612 | 9q33-q34    |
|                                        |                     | transforming growth factor, beta receptor II (70-80kD)/TGFBRII                                    | 190182 | NM_003242 | 3p22        |
|                                        |                     | transforming growth factor, beta receptor III (betaglycan, 300kD)/TGFBRIII                        | 600742 | NM_003243 | 1p33-p32    |
|                                        |                     | heparin-binding growth factor 1/FGF1                                                              | 131220 | NM_000800 | 5q31        |
|                                        |                     | basic fibroblast growth factor/FGF2                                                               | 134920 | NM_002006 | 4q25-q27    |
| <b>Biosynthesis</b>                    |                     | fibroblast growth factor 3/FGF3                                                                   | 164950 | NM_005247 | 11q13       |
|                                        |                     | HST oncogene/fibroblast growth factor 4/FGF4                                                      | 164980 | NM_002008 | 11q13       |
|                                        |                     | fibroblast growth factor-related protein/FGF5                                                     | 165190 | NM_004464 | 4q21        |
|                                        |                     | fibroblast growth factor 6/FGF6                                                                   | 134921 | X57075    | 12p13       |
|                                        |                     | keratinocyte growth factor/fibroblast growth factor 7/FGF7                                        | 148180 | NM_002009 | 15q15-q21.1 |
|                                        |                     | fibroblast growth factor 8 (androgen-induced)/FGF8                                                | 600483 | NM_006119 | 10q24       |
|                                        |                     | fibroblast growth factor 9 (glia-activating factor)/FGF9                                          | 600921 | NM_002010 | 13q11-q12   |
|                                        |                     | fibroblast growth factor 10/FGF10                                                                 | 602115 | NM_004465 | 5p13-p12    |
|                                        |                     | fibroblast growth factor 11/FGF11                                                                 | 601514 | NM_004112 | 17q21       |
|                                        |                     | fibroblast growth factor 12/FGF12                                                                 | 601513 | *****     | 3q28        |
|                                        |                     | fibroblast growth factor 13/FGF13                                                                 | 300070 | NM_004114 | Xq26.3      |
| <b>Fibroblast Growth Factor</b>        |                     |                                                                                                   |        |           |             |



|                       |                                                                                                                                                                                                    |        |           |              |
|-----------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------|-----------|--------------|
| <b>Growth Factor</b>  | fibroblast growth factor 14/FGF14                                                                                                                                                                  | 601515 | NM_004115 | 13q34        |
|                       | fibroblast growth factor 16/FGF16                                                                                                                                                                  | 603724 | NM_003868 | *****        |
|                       | fibroblast growth factor 17/FGF17                                                                                                                                                                  | 603725 | NM_003867 | 8p21         |
|                       | fibroblast growth factor 18/FGF18                                                                                                                                                                  | 603726 | NM_003862 | *****        |
|                       | fibroblast growth factor 19/FGF19                                                                                                                                                                  | 603891 | NM_005117 | *****        |
| <b>Growth Factors</b> | fibroblast growth factor receptor 1/FGFR1                                                                                                                                                          | 136350 | *****     | 8p11.2-p11.1 |
|                       | fibroblast growth factor receptor 2 (bacteria-expressed kinase, keratinocyte growth factor receptor, craniofacial dysostosis 1, Crouzon syndrome, Pfeiffer syndrome, Jackson-Weiss syndrome)/FGFR2 | 176943 | NM_000141 | 10q26        |
|                       | fibroblast growth factor receptor 3 (achondroplasia, thanatophoric dwarfism)/FGFR3                                                                                                                 | 134934 | NM_005247 | 4p16.3       |
|                       | fibroblast growth factor receptor 4/FGFR4                                                                                                                                                          | 134935 | NM_002011 | 5q35.1-qter  |
|                       | somatostatin transcription factor 1/STF1/homeodomain transcription factor/insulin promoter factor 1/IPF1                                                                                           | 600733 | NM_000209 | 13q12.1      |
|                       | paired box gene 6/PAX6                                                                                                                                                                             | 106210 | NM_000280 | 11p13        |
|                       | somatostatin/SST                                                                                                                                                                                   | 182450 | NM_001048 | 3q28         |
|                       | preprocratistatin/CORT                                                                                                                                                                             | 602784 | NM_001302 | 1p36         |
|                       | Somatostatin receptor 1/G protein-coupled/SSTR1                                                                                                                                                    | 182451 | NM_001049 | 14q13        |
|                       | Somatostatin receptor 2/SSTR2                                                                                                                                                                      | 182452 | NM_001050 | 17q24        |
| <b>Somatostatin</b>   |                                                                                                                                                                                                    |        |           |              |
| <b>Biosynthesis</b>   |                                                                                                                                                                                                    |        |           |              |
| <b>Receptors</b>      |                                                                                                                                                                                                    |        |           |              |

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|                | <b>Receptors</b>    | Somatostatin receptor 3/adenyl cyclase coupled/SSTR3                                                        | 182453 | NM_001051 | 22q13.1       |
|                |                     | Somatostatin receptor 4/SSTR4                                                                               | 182454 | NM_001052 | 20p11.2       |
|                |                     | Somatostatin receptor 5/SSTR5                                                                               | 182455 | NM_001053 | 16p13.3       |
| <b>Insulin</b> | <b>Biosynthesis</b> | somatostatin transcription factor 1/STF1/homeodomain transcription factor/insulin promoter factor 1/IPF1    | 600733 | NM_000209 | 13q12.1       |
|                |                     | insulin/INS                                                                                                 | 176730 | NM_000207 | 11p15.5       |
|                |                     | sulfonylurea receptor (hyperinsulinemia)/SUR                                                                | 600509 | NM_000352 | 11p15.1       |
|                |                     | beta-cell inward rectifier subunit/BIR/potassium inwardly-rectifying channel, subfamily J, member 11/KCNJ11 | 600937 | D50582    | 11p15.1       |
|                |                     | carboxypeptidase E/CPE                                                                                      | 114855 | NM_001873 | Chr.4         |
|                | <b>Receptor</b>     | insulin receptor/INSR                                                                                       | 147670 | NM_000208 | 19p13.2       |
|                |                     | insulin receptor substrate 1/IRS1                                                                           | 147545 | NM_005544 | 2q36          |
|                |                     | insulin receptor substrate 2/IRS2                                                                           | 600797 | NM_003749 | 13q34         |
|                |                     | insulin receptor substrate 4/IRS4                                                                           | 603510 | NM_003604 | *****         |
|                | <b>Signaling</b>    | amylin/diabetes-associated peptide/DAP/islet amyloid polypeptide/IAPP                                       | 147940 | NM_000415 | 12p12.3-p12.1 |
|                | <b>Metabolism</b>   | insulin-degrading enzyme/IDE                                                                                | 146680 | NM_004969 | 10q23-q25     |
|                | <b>Diagonosis</b>   | insulin-like growth factor 1 (somatomedin C)/IGF1                                                           | 147440 | M27544    | 12q22-q24.1   |

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| <b>Biosynthesis</b>               | insulin-like growth factor 2 (somatomedin A)/IGF2                | 147470 | NM_000612             | 11p15.5      |
|                                   | insulin-like growth factor 1 receptor precursor/IGF1R            | 147370 | NM_000875             | 15q25-q26    |
| <b>Receptors</b>                  | insulin-like growth factor 2 receptor/IGF2R                      | 147280 | NM_000876             | 6q26         |
|                                   | insulin-like growth factor binding protein                       | 146730 | NM_000596             | 7p14-p12     |
| <b>Insulin-Like Growth Factor</b> | insulin-like growth factor binding protein                       | 146731 | M35410                | 2q33-q34     |
|                                   | insulin-like growth factor binding protein                       | 146732 | NM_000598             | 7p14-p12     |
|                                   | insulin-like growth factor binding protein                       | 146733 | Y12508                | 17q12-q21    |
|                                   | insulin-like growth factor binding protein                       | 146734 | AF055033              | 2q33-q36     |
|                                   | insulin-like growth factor binding protein                       | 146735 | M69054                | 12q13        |
|                                   | insulin-like growth factor binding protein                       | 602867 | NM_001553             | 4q12         |
|                                   | connective tissue growth factor/CTGF                             | 121009 | NM_001901             | 6q23.1       |
|                                   | insulin-like growth factor binding protein                       | 602369 | NM_001554             | 1p22.3       |
|                                   | insulin-like growth factor binding protein                       | 601489 | NM_004970             | Chr. 16      |
|                                   | protease, serine, 11 (IGF binding)/PRSS11                        | 602194 | NM_002775             | 0q25.3-q26.2 |
| <b>Catabolism</b>                 | angiopoietin 1/ANGPT1                                            | 601667 | NM_00114 <sub>6</sub> | 8q22         |
|                                   | angiopoietin 2/ANGPT2                                            | 601922 | NM_00114 <sub>7</sub> | 8p21         |
| <b>Biosynthesis</b>               | angiopoietin 3/ANGPT3                                            | 603874 | NM_00467 <sub>3</sub> | *****        |
|                                   | angiopoietin 4/ANGPT4                                            | 603705 | AF113708              | 20p13        |
|                                   | angiopoietin 5/ANGPT5                                            | *****  | AF152562              | *****        |
|                                   | protein receptor tyrosine kinase, epithelial-specific 2/TIE2/TEK | 600221 | NM_00045 <sub>9</sub> | 9p21         |
| <b>Receptors</b>                  | tyrosine kinase, endothelial/TEK                                 |        |                       |              |
| <b>Angiopoietin</b>               |                                                                  |        |                       |              |
|                                   |                                                                  |        |                       |              |

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| Platelet-Derived Growth Factor | Biosynthesis                  | platelet-derived growth factor alpha polypeptide/PDGFA                                                | 173430 | NM_002607 | 7p22         |
|                                |                               | platelet-derived growth factor beta polypeptide (simian sarcoma viral (v-sis) oncogene homolog)/PDGFB | 190040 | NM_002608 | 2q12.3-q13.1 |
|                                | Receptors                     | platelet-derived growth factor receptor, alpha polypeptide/PDGFR                                      | 173490 | NM_006206 | 4q12         |
|                                |                               | platelet-derived growth factor receptor, beta polypeptide/PDGFRB                                      | 173410 | NM_002609 | 5q31-q32     |
| Phosphodiesterases             |                               | phosphodiesterase 1A, calmodulin-dependent/PDE1A                                                      | 171890 | NM_005019 | Chr.4        |
|                                |                               | phosphodiesterase 1B, calmodulin-dependent/PDE1B                                                      | 171891 | NM_000924 | 12q13        |
|                                |                               | phosphodiesterase 1C, calmodulin-dependent/PDE1C                                                      | 602987 | NM_005020 | *****        |
|                                |                               | phosphodiesterase 3A, cGMP-inhibited/PDE3A                                                            | 123805 | NM_000921 | 11p15        |
|                                |                               | phosphodiesterase 3B, cGMP-inhibited/PDE3B                                                            | 602047 | NM_000922 | 11p15        |
|                                |                               | phosphodiesterase 5A, cGMP-specific/PDE5A                                                             | 603310 | NM_001083 | 4q26         |
|                                | AMP-Activated Protein Kinases | protein kinase, AMP-activated, alpha 1                                                                | 602739 | NM_006251 | 5p12         |
|                                |                               | protein kinase, AMP-activated, beta 1                                                                 | 602740 | NM_006253 | 12q24.1      |
|                                |                               | protein kinase, AMP-activated, gamma                                                                  | 602742 | NM_002733 | 12q13.1      |
|                                |                               | protein kinase, AMP-activated, alpha 2 catalytic subunit/PRKAA2                                       | 600497 | NM_006252 | 1p31         |
|                                |                               | protein kinase, AMP-activated, beta 2 non-catalytic subunit/PRKAB2                                    | 602741 | NM_005399 | *****        |

|                                |                                                                                                    |        |           |              |
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|                                | protein kinase, ADP-activated, gamma 2 non-catalytic subunit                                       | 602743 | *****     | 7q35-q36     |
| cGMP-Dependent Protein Kinases | protein kinase, cGMP-dependent, regulatory, type I/PRKG1                                           | 176894 | D45864    | 10q11.2      |
|                                | protein kinase, cGMP-dependent, type II/PRKG2                                                      | 601591 | NM_006259 | 4q13.1-q21.1 |
|                                | protein kinase, cAMP-dependent, regulatory, type I, alpha (tissue specific extinguisher 1)/PRKAR1A | 188830 | NM_002734 | 17q23-q24    |
| cAMP-Activated Protein Kinases | protein kinase, cAMP-dependent, regulatory, type I, beta/PRKAR1B                                   | 176911 | *****     | 7pter-p22    |
|                                | protein kinase, cAMP-dependent, regulatory, type II, alpha/PRKAR2A                                 | 176910 | NM_004157 | 3p21.3-p21.2 |
|                                | protein kinase, cAMP-dependent, regulatory, type II, beta/PRKAR2B                                  | 176912 | NM_002736 | 7q22         |
|                                | protein kinase, cAMP-dependent, catalytic, alpha/PRKACA                                            | 601639 | NM_002730 | 19p13.1      |
|                                | protein kinase, cAMP-dependent, catalytic, beta/PRKACB                                             | 176892 | NM_002731 | 1p36.1       |
|                                | protein kinase, cAMP-dependent, catalytic, gamma/PRKACG                                            | 176893 | NM_002732 | 9q13         |
|                                | guanine nucleotide binding protein (G protein), alpha 11 (Gq class)/GNA11                          | 139313 | NM_002067 | 19p13        |
|                                | guanine nucleotide binding protein (G protein), alpha 13/GNA13                                     | *****  | NM_006572 | *****        |
|                                | guanine nucleotide-binding protein (G protein), alpha 14 /GNA14                                    | *****  | NM_004297 | *****        |
|                                | guanine nucleotide binding protein (G protein), alpha 15 (Gq class)/GNA15                          | 139314 | NM_002068 | 19p13        |

|                                                                                                              |        |            |                 |
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| guanine nucleotide binding protein (G protein), alpha activating activity polypeptide L, olfactory type/GNAL | 139312 | NM_00207_1 | 18p11.22-p11.21 |
| guanine nucleotide binding protein (G protein), alpha activating activity polypeptide O/GNAO1                | 139311 | Y18213     | 16q13           |
| guanine nucleotide binding protein (G protein), q polypeptide/GNAQ                                           | 600998 | NM_00207_2 | 9q21            |
| guanine nucleotide binding protein (G protein), alpha z polypeptide/GNAZ                                     | 139160 | NM_00207_3 | 22q11.2         |
| guanine nucleotide binding protein (G protein), beta polypeptide 1/GNB1                                      | 139380 | *****      | 1pter-p31.2     |
| guanine nucleotide binding protein (G protein), beta polypeptide 2/GNB2                                      | 139390 | NM_00527_3 | 7q21-q27        |
| guanine nucleotide binding protein (G protein), beta polypeptide 2-like 1/GNB2L1/RACK1                       | 176981 | NM_00609_8 | *****           |
| guanine nucleotide binding protein (G protein), beta polypeptide 3/GNB3                                      | 139130 | NM_00207_5 | 12p13           |
| guanine nucleotide binding protein (G protein), beta 5/GNB5                                                  | *****  | NM_00657_8 | *****           |
| guanine nucleotide binding protein (G protein), gamma 3/GNG3                                                 | *****  | AF188177   | *****           |
| guanine nucleotide binding protein (G protein), gamma 4/GNG4                                                 | *****  | NM_00448_5 | *****           |
| guanine nucleotide binding protein (G protein), gamma 5/GNG5                                                 | 600874 | NM_00527_4 | 1p22            |
| guanine nucleotide binding protein (G protein), gamma 7/GNG7                                                 | *****  | NM_00514_5 | *****           |

### G-Proteins

### Second Messengers

|                                 |                                                                                                |        |           |             |
|---------------------------------|------------------------------------------------------------------------------------------------|--------|-----------|-------------|
|                                 | guanine nucleotide binding protein (G protein), gamma 8/GNG8                                   | *****  | AF188179  | *****       |
|                                 | guanine nucleotide binding protein (G protein), gamma 10/GNG10                                 | *****  | NM_004125 | *****       |
|                                 | guanine nucleotide binding protein (G protein), gamma 11/GNG11                                 | *****  | NM_004126 | *****       |
|                                 | guanine nucleotide binding protein (G protein), gamma 12/GNG12                                 | *****  | AF188181  | *****       |
| <b>G-Protein Modulators</b>     | guanine nucleotide binding protein (G protein), alpha stimulating activity polypeptide 1/GNAS1 | 139320 | NM_000516 | 20q13.2     |
|                                 | guanine nucleotide binding protein (G protein), alpha inhibiting activity polypeptide 1/GNAI1  | 139310 | NM_002069 | 7q21        |
|                                 | guanine nucleotide binding protein (G protein), alpha inhibiting activity polypeptide 2/GNAI2  | 139360 | NM_002070 | 3p21        |
|                                 | guanine nucleotide binding protein (G protein), alpha inhibiting activity polypeptide 3/GNAI3  | 139370 | NM_006496 | 1p13        |
|                                 | guanine nucleotide binding protein (G protein), alpha inhibiting activity polypeptide H/GNAIH  | 139180 | *****     | 12p13-p12   |
|                                 | v-src avian sarcoma (Schmidt-Ruppin A-2) viral oncogene homolog/SRC                            | 190090 | NM_005417 | 20q12-q13   |
| <b>Protein Tyrosine Kinases</b> | protein kinase C alpha/PRKCA                                                                   | 176960 | NM_002737 | 17q22-q23.2 |
|                                 | protein kinase C beta/PRKCB                                                                    | 176970 | X06318    | 16p11.2     |

|                                                                                      |                                                                   |        |           |           |
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| <b>Calcium-<br/>and<br/>Diacylglycerol-<br/>Activated<br/>Protein<br/>Kinases</b>    | protein kinase C, delta/PRKCD                                     | 176977 | NM_006254 | 3p        |
|                                                                                      | protein kinase C, epsilon/PRKCE                                   | 176975 | NM_005400 | 2p21      |
|                                                                                      | protein kinase C gamma/PRKCG                                      | 176980 | *****     | 19q13.4   |
|                                                                                      | protein kinase C, iota/PRKCI                                      | 300094 | NM_002740 | Xq21.3    |
|                                                                                      | protein kinase C, mu/PRKCM                                        | *****  | NM_002742 | *****     |
|                                                                                      | protein kinase C, theta/PRKCT                                     | 600448 | NM_006257 | 10p15     |
| <b>(Ca<sup>++</sup>)-<br/>Calmodulin-<br/>Dependent<br/>Protein<br/>Phosphatases</b> | protein kinase C, zeta/PRKCZ                                      | 176982 | NM_002744 | *****     |
|                                                                                      | protein phosphatase 3, catalytic subunit A, alpha isoform/PPP3CA  | 114105 | M29550    | 4q21-q24  |
|                                                                                      | protein phosphatase 3, catalytic subunit A, beta isoform/PPP3CB   | 114106 | M29551    | 10q21-q22 |
|                                                                                      | protein phosphatase 3, regulatory subunit B, alpha isoform/PPP3CB | 601302 | *****     | 2p16-p15  |
|                                                                                      | mitogen activated protein kinase PRKM1/MAPK1/ERK2                 | 176948 | NM_002745 | 22q11.2   |
|                                                                                      | mitogen activated protein kinase PRKM3/MAPK3/ERK1                 | 601795 | X60188    | 16p11.2   |
| <b>Mitogen<br/>Activated</b>                                                         | mitogen activated protein kinase PRKM4/MAPK4                      | 176949 | NM_002747 | 18q12-q21 |
|                                                                                      | mitogen activated protein kinase PRKM6/MAPK6                      | 602904 | NM_002748 | *****     |
|                                                                                      | mitogen activated protein kinase PRKM7/MAPK7                      | 602521 | NM_002749 | 17p11.2   |
|                                                                                      | mitogen activated protein kinase JNK1/PRKM8/MAPK8                 | 601158 | L26318    | *****     |
|                                                                                      |                                                                   |        |           |           |

**Growth  
Control**  
(*additional  
genes in  
Oncology*)



**kinases**

|                                                        |        |               |                   |
|--------------------------------------------------------|--------|---------------|-------------------|
| mitogen activated protein kinase<br>JNK2/PRKM9/MAPK9   | 602896 | U09759        | 5q35              |
| mitogen activated protein kinase<br>JNK3/PRKM10/MAPK10 | 602897 | U35003        | *****             |
| mitogen activated protein kinase<br>PRKM11/MAPK11      | 602898 | AF031135      | *****             |
| mitogen activated protein kinase<br>SAPK3/MAPK12       | 602399 | NM_00296<br>9 | 22q13.3           |
| mitogen activated protein kinase<br>PRKM13/MAPK13      | 602899 | NM_00275<br>4 | *****             |
| mitogen activated protein kinase<br>SAPK2A/MAPK14      | 600289 | NM_00131<br>5 | 6p21.3-<br>p21.2  |
| BCL2                                                   | 151430 | M13994        | 18q21.3           |
| BCL-X/BCLX                                             | 600039 | Z23115        | *****             |
| BCL2 associated protein/BAX                            | 600040 | L22473        | 19q13.3-<br>q13.4 |
| BCL2-antagonist/killer 1/BAK1                          | 600516 | NM_00118<br>8 | 6p21.3-<br>p21.2  |
| BCL2-associated athanogene 1/BAG1                      | 601497 | NM_00432<br>3 | 9p12              |
| BCL2-associated athanogene 2/BAG2                      | 603882 | NM_00428<br>2 | *****             |
| BCL2-associated athanogene 3/BAG3                      | 603883 | AF095193      | *****             |
| BCL2-associated athanogene 4/BAG4                      | 603884 | AF095194      | *****             |
| BCL2-associated athanogene 5/BAG5                      | 603885 | AF095195      | *****             |
| BCL-X/BCL-2 binding protein/BAD                        | 603167 | AF021792      | *****             |
| BCL2-like 1/BCL2L1                                     | 600039 | NM_00119<br>1 | *****             |
| BCL2-like 2/BCL2L2                                     | 601931 | NM_00405<br>0 | 14q11.2-<br>q12   |

|                                                       |        |           |                  |
|-------------------------------------------------------|--------|-----------|------------------|
| BCL2-like 11 (apoptosis facilitator)/BCL2L11          | 603827 | NM_006538 | *****            |
| BCL2-related protein A1/BCL2A1                        | 601056 | Y09397    | 15q24.3          |
| BCL2-interacting protein harikari/HRK                 | 603447 | NM_003806 | *****            |
| BCL-2 interacting killer/BIK                          | 603392 | U34584    | *****            |
| v-raf-1 murine leukemia viral oncogene homolog 1/RAF1 | 164760 | NM_002880 | 3p25             |
| tumor protein p53/TP53                                | 191170 | X02469    | 17p13.1          |
| superfamily, member 6/FAS/TNFRSF6                     | 134637 | NM_000043 | 10q24.1          |
| nuclear factor kappa-B DNA binding subunit 1/NFKB1    | 164011 | M58603    | 4q23-q24         |
| nuclear factor kappa-B DNA binding subunit 2/NFKB2    | 164012 | NM_002502 | 10q24            |
| apoptosis-related cysteine protease 1/caspase 1/CASP1 | 147678 | L27475    | 11q22.2-q22.3    |
| apoptosis-related cysteine protease 1/caspase 1/CASP2 | 600639 | *****     | 7q35             |
| apoptosis-related cysteine protease 1/caspase 1/CASP3 | 600636 | NM_004346 | 4q35, 4q33-q35.1 |
| apoptosis-related cysteine protease 1/caspase 1/CASP4 | 602664 | NM_004347 | 11q22.2-q22.3    |
| apoptosis-related cysteine protease 1/caspase 1/CASP5 | 602665 | NM_004347 | 11q22.2-q22.3    |
| apoptosis-related cysteine protease 1/caspase 1/CASP6 | 601532 | NM_001226 | 4q25-q25         |
| apoptosis-related cysteine protease 1/caspase 1/CASP7 | 601761 | NM_001227 | 10q25.1-q25.2    |

## Apoptosis

## Apoptosis

|            |            |                                                                                           |        |           |            |
|------------|------------|-------------------------------------------------------------------------------------------|--------|-----------|------------|
|            |            | apoptosis-related cysteine protease<br>1/caspase 1/CASP8                                  | 601763 | NM_001228 | 2q33-q34   |
|            |            | apoptosis-related cysteine protease<br>1/caspase 1/CASP9                                  | 602234 | *****     | *****      |
|            |            | apoptosis-related cysteine protease<br>1/caspase 1/CASP10                                 | 601762 | NM_001230 | 2q33-q34   |
|            |            | apoptosis-related cysteine protease<br>1/caspase 1/CASP13                                 | 603653 | NM_003723 | *****      |
|            |            | ADP-ribosyltransferase (NAD <sup>+</sup> ; poly<br>(ADP-ribose)<br>polymerase)/PARP/ADPRT | 173870 | NM_001618 | 1q42       |
|            |            | poly (ADP-ribose)<br>glycohydrolase/PARG                                                  | 603501 | NM_003631 | 10q11.23   |
|            |            | cyclin-dependent kinase (CDK2)                                                            | 116953 | NM_001798 | 12q13      |
|            |            | cyclin-dependent kinase (CDK3)                                                            | 123828 | NM_001258 | 17q22-qter |
|            |            | cyclin-dependent kinase (CDK4)                                                            | 123829 | NM_000075 | 12q14      |
|            |            | cyclin-dependent kinase (CDK5)                                                            | 123831 | NM_004935 | 7q36       |
|            |            | cyclin-dependent kinase (CDK6)                                                            | 603368 | NM_001259 | 7q21-q22   |
|            |            | cyclin-dependent kinase (CDK7)                                                            | 601955 | NM_003157 | 2p15-cen   |
|            |            | cyclin-dependent kinase (CDK8)                                                            | 603184 | NM_001260 | 13q12      |
|            |            | cyclin-dependent kinase (CDK9)                                                            | 603251 | NM_001261 | 9q34.1     |
|            |            | E2F transcription factor 1/E2F1                                                           | 189971 | M96577    | 20q11.2    |
| Cell Cycle | Cell Cycle |                                                                                           |        |           |            |

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| <b>General<br/>Steroid<br/>Hormone<br/>Metabolism<br/>(additional<br/>genes in<br/>Toxicology)</b> | steroid-5-alpha-reductase, alpha polypeptide 1 (3-oxo-5 alpha-steroid delta 4-dehydrogenase alpha 1)/SRD5A1 | 184753 | NM_001047 | 5p15      |
|                                                                                                    | steroid-5-alpha-reductase, alpha polypeptide 2 (3-oxo-5 alpha-steroid delta 4-dehydrogenase alpha 2)/SRD5A2 | 264600 | NM_000348 | 2p23      |
|                                                                                                    | steroidogenic acute regulatory protein/STAR                                                                 | 600617 | NM_000349 | 8p11.2    |
|                                                                                                    | cytochrome P450, subfamily XIA (cholesterol side chain cleavage)/CYP11A                                     | 118485 | NM_000781 | 15q23-q24 |
|                                                                                                    | cytochrome P450, subfamily XVII (steroid 17-alpha-hydroxylase), adrenal hyperplasia/CYP17                   | 202110 | NM_000102 | 10q24.3   |
|                                                                                                    | hydroxy-delta-5-steroid dehydrogenase, 3 beta- and steroid delta-isomerase 1/HSD3B1                         | 109715 | NM_000862 | 1p13.1    |
|                                                                                                    | hydroxy-delta-5-steroid dehydrogenase, 3 beta- and steroid delta-isomerase 2/HSD3B2                         | 201810 | NM_000198 | 1p13.1    |
|                                                                                                    | dehydroepiandrosterone (DHEA)-preferring sulfotransferase, family 2A, member 1/SULT2A1                      | 125263 | NM_003167 | 19q13.3   |
|                                                                                                    | estrogen-preferring                                                                                         | 600043 | NM_005420 | 4q13.1    |
|                                                                                                    | UDP glycosyltransferase 1/UGT1                                                                              | 191740 | NM_001072 | Chr. 12   |
|                                                                                                    | UDP glycosyltransferase family 2, member B4/UGT2B4                                                          | 600067 | NM_001073 | 4q13      |
|                                                                                                    | <b>Catabolism</b>                                                                                           |        |           |           |
|                                                                                                    |                                                                                                             |        |           |           |
|                                                                                                    |                                                                                                             |        |           |           |

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| Biosynthesis | UDP glycosyltransferase family 2, member B7/UGT2B7                            | 600068 | NM_001074 | 1q14          |
|              | UDP glycosyltransferase 2 family, polypeptide B11/UGT2B11                     | 603064 | NM_001073 | *****         |
|              | UDP glycosyltransferase family 2, member B15/UGT2B15                          | 600069 | NM_001076 | 4q13          |
|              | UDP glycosyltransferase family 2, member B17/UGT2B17                          | 601903 | NM_001077 | 1q14          |
| Biosynthesis | acetyl-Coenzyme A carboxylase alpha/ACACA                                     | 200350 | NM_000664 | 17q21         |
|              | acetyl-Coenzyme A carboxylase beta/ACACB                                      | 601557 | NM_001093 | 12q24.1       |
|              | acetyl-Coenzyme A acetyltransferase 1 (acetoacetyl Coenzyme A thiolase)/ACAT1 | 203750 | NM_000019 | 11q22.3-q23.1 |
|              | acetyl-Coenzyme A acetyltransferase 2 (acetoacetyl Coenzyme A thiolase)/ACAT2 | 100678 | NM_005891 | 6q25.3-q26    |
|              | ATP citrate lyase/ACLY                                                        | 108728 | NM_001096 | 17q21.1       |
|              | glycerol-3-phosphate acyltransferase, mitochondrial/GPAM1                     | 602395 | *****     | 10q24-q26     |
|              | fatty acid synthase/FASN                                                      | 600212 | NM_004104 | 17q25         |
|              | apolipoprotein A1 of HDL/APOA1                                                | 107680 | NM_000039 | 11q23         |
|              | apolipoprotein A2/APOA2                                                       | 107670 | NM_001643 | 1q21-q23      |
|              | apolipoprotein A4/APOA4                                                       | 107690 | NM_000482 | 11q23         |
|              | apolipoprotein B (including Ag(x) antigen)/APOB                               | 107730 | NM_000384 | 2p24          |

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| <b>Lipid<br/>Metabolism<br/>and Storage</b> | apolipoprotein B mRNA editing<br>enzyme, catalytic polypeptide                                                                  | 600130 | NM_005889     | 12p13.1      |
|                                             | APOBEC1 binding<br>protein/ABBP1/heterogeneous nuclear<br>ribonucleoprotein A/B/HNRPAB                                          | 602688 | NM_004499     | *****        |
|                                             | apolipoprotein C1/APOC1                                                                                                         | 107710 | NM_001645     | 19q13.2      |
|                                             | apolipoprotein C2/APOC2                                                                                                         | 207750 | NM_000483     | 19q13.2...   |
|                                             | apolipoprotein C3/APOC3                                                                                                         | 107720 | NM_000040     | 11q23        |
|                                             | apolipoprotein C4/APOC4                                                                                                         | 600745 | NM_001646     | 19q13.2      |
|                                             | apolipoprotein D/APOD                                                                                                           | 107740 | NM_001647     | 3q26.2-qter  |
|                                             | apolipoprotein E/APOE                                                                                                           | 107741 | NM_000041     | 19q13.2      |
|                                             | apolipoprotein F/APOF                                                                                                           | 107760 | NM_001638     | Chr.12       |
|                                             | apolipoprotein H (beta-2-glycoprotein<br>I)/APOH                                                                                | 138700 | NM_000042     | 17q23-qter   |
|                                             | apolipoprotein J/clustrin/APOJ/CLU                                                                                              | 185430 | NM_001831     | 8p21-p12     |
|                                             | apolipoprotein L/APOL                                                                                                           | 603743 | AF019225      | Chr. 22      |
|                                             | pancreatic triglyceride lipase/PNLIP                                                                                            | 246600 | AH003527      | 10q26.1      |
|                                             | enterostatin/colipase, pancreatic/CLPS                                                                                          | 120105 | NM_001832     | 6pter-p21.1  |
|                                             | high density lipoprotein<br>receptor/CD36 antigen (collagen type I<br>receptor, thrombospondin receptor)-<br>like 1/CD36L1/SRB1 | 601040 | NM_00550<br>5 | Chr. 12      |
|                                             | cubilin (intrinsic factor-cobalamin<br>receptor) precursor/CUBN                                                                 | 602997 | NM_00108<br>1 | 10p12.1      |
| <b>Transport</b>                            | cholesterol efflux regulatory protein/CE<br>low density lipoprotein receptor<br>(familial hypercholesterolemia)/LDLR            | 600046 | NM_005502     | 9q22-q31     |
|                                             | low density lipoprotein receptor-<br>related protein 1/LRP1                                                                     | 143890 | NM_000527     | 9p13.2-p13.1 |
|                                             |                                                                                                                                 | 107770 | NM_002332     | 2q13.1-q13.3 |

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| <b>Uptake</b>  | low density lipoprotein receptor-related protein 2/LRP2             | 600073 | U33837    | 2q24-q31     |
|                | low density lipoprotein receptor-related protein 5/LRP5             | 603506 | AF077820  | 11q13.4      |
|                | low density lipoprotein receptor-related protein 8/LRP8             | 602600 | NM_004631 | 1p34         |
|                | low density lipoprotein receptor-related protein-associated protein | 104225 | NM_002337 | 4p16.3       |
|                | oxidized low density lipoprotein receptor/OLR1                      | 602601 | NM_002543 | 12p13-p12    |
|                | very low density lipoprotein receptor/VLDLR                         | 192977 | NM_003383 | 9p24         |
|                | microsomal triglyceride transfer protein large subunit/MTP          | 157147 | NM_000253 | 4q22-q24     |
|                | sortilin related receptor/SORL1                                     | 602005 | NM_003105 | 1q23.2-q24.2 |
|                | plasma cholesterol ester transfer protein/CETP                      | 118470 | NM_000078 | 16q21        |
|                | phospholipid transfer protein/PLTP                                  | 172425 | NM_006227 | 20q12-q13.1  |
|                | glycerol-3-phosphate acyltransferase, mitochondrial/GPAM1           | 602395 | *****     | 10q24-q26    |
|                | lipoprotein lipase/LPL                                              | 238600 | NM_000237 | 8p22         |
|                | lipase, hepatic/LIPC                                                | 151670 | NM_000236 | 15q21-q23    |
|                | adrenergic, beta-3-, receptor/ADRB3                                 | 109691 | NM_000025 | 8p12-p11.2   |
| <b>Storage</b> | lysosomal acid lipase/LIPB                                          | 278000 | NM_000235 | 10q24-q25    |
|                | lipase, hormone-sensitive/LIPE                                      | 151750 | NM_005357 | 9q13.1-q13.2 |
|                | perilipin/PLIN                                                      | 170290 | NM_002666 | 15q26        |
|                | fatty acid binding protein 4, adipocyte/FABP4                       | 600434 | NM_001442 | 8q21         |
|                |                                                                     |        |           |              |
| <b>Release</b> |                                                                     |        |           |              |
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**Lipid Metabolism**



|                           |                                                                                                |        |            |            |
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| <b>Coenzyme A Ligases</b> | Fatty acid CoA Ligase, long chain 1/FACL1                                                      | 152425 | *****      | 3q13       |
|                           | Fatty acid CoA Ligase, long chain 2/FACL2                                                      | 152426 | *****      | 4q34-q35   |
|                           | Fatty acid CoA Ligase, long chain 3/FACL3                                                      | 602371 | NM_004457  | 2q34-q35   |
|                           | Fatty acid CoA Ligase, long chain 4/FACL4                                                      | 300157 | NM_004458  | Xq22.3     |
|                           | Fatty acid CoA Ligase, very long chain 1/FACVLI                                                | 603247 | NM_003645  | 15q21.2    |
| <b>Ketogenesis</b>        | 3-hydroxy-3-methylglutaryl-Coenzyme A synthase 2                                               | 600234 | NM_005518  | 1p13-p12   |
|                           | acyl-Coenzyme A dehydrogenase, long                                                            | 201460 | NM_001608  | 2q34-q35   |
|                           | acyl-Coenzyme A dehydrogenase, C-4                                                             | 201450 | NM_000016  | 1p31       |
|                           | acyl-Coenzyme A dehydrogenase, C-2                                                             | 201470 | NM_000017  | 12q22-qter |
|                           | carnitine palmitoyltransferase I, liver, nuclear gene encoding mitochondrial protein/CPT1A     | 600528 | NM_001876  | 11q13      |
|                           | carnitine palmitoyltransferase II, nuclear gene encoding mitochondrial protein/CPT2            | 600650 | NM_000098  | 1p32       |
|                           | carnitine/acylcarnitine                                                                        | 212138 | NM_000387  | 3p21.31    |
|                           | enoyl-CoA, hydratase/3-hydroxyacyl CoA dehydrogenase/EHHADH                                    | 261515 | NM_001966  | 3q27       |
|                           | hydroxyacyl-CoA dehydrogenase/3-ketoacyl-CoA thiolase/enoyl-CoA hydratase, alpha subunit/HADHA | 600890 | NM_0000182 | 2p23       |
|                           |                                                                                                |        |            |            |
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| <b>β-Oxidation</b>             | hydroxyacyl-CoA dehydrogenase/3-ketoacyl-CoA thiolase/enoyl-CoA hydratase, beta subunit/HADHB | 143450 | NM_000183 | 2p23        |
|                                | acyl-Coenzyme A oxidase 1/ACOX1 (peroxisomal)                                                 | 264470 | NM_004035 | 17q25       |
|                                | acyl-Coenzyme A oxidase 2, branched chain/ACOX2 (peroxisomal)                                 | 601641 | NM_003500 | 3p14.3      |
|                                | acyl-Coenzyme A dehydrogenase, C-2 to C-3 short chain precursor/ACADS (mitochondrial)         | 201470 | NM_000017 | 12q22-qter  |
|                                | acyl-Coenzyme A dehydrogenase, C-4 to C-12 straight chain/ACADM (mitochondrial)               | 201450 | NM_000016 | 1p31        |
|                                | acyl-Coenzyme A dehydrogenase, long chain/ACADL (mitochondrial)                               | 201460 | NM_001608 | 2q34-q35    |
|                                | hydroxyacyl-Coenzyme A dehydrogenase, type II/HADH2                                           | 602057 | NM_004493 | *****       |
|                                | enoyl-Coenzyme A hydratase 1/ECH1 (peroxisomal)                                               | 600696 | NM_001398 | 19q13       |
|                                | cystathionine-beta-synthase/CBS                                                               | 236200 | NM_000071 | 21q22.3     |
|                                | cubilin (intrinsic factor-cobalamin receptor) precursor/CUBN                                  | 602997 | NM_001081 | 10p12.1     |
| <b>Homocysteine Metabolism</b> | betaine-homocysteine S-methyltransferase/BHMT                                                 | 602888 | NM_001713 | *****       |
|                                | 5-methyltetrahydrofolate-homocysteine methyltransferase/methionine                            | 156570 | NM_000254 | 1q43        |
|                                | S-adenosylhomocysteine hydrolase/AHCY                                                         | 180960 | M61832    | 20cen-q13.1 |

|  |                         |                                     |                                                                       |        |           |              |
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|  |                         |                                     | methylenetetrahydrofolate reductase/MTHFR                             | 236250 | AH007464  | 1p36.3       |
|  | Purine Nucleotide Cycle | Purine Nucleotide Cycle             | adenosine monophosphate deaminase 1 (isoform M)/AMPD1                 | 102770 | NM_000036 | 1p21-p13     |
|  |                         |                                     | adenylosuccinate synthase/ADSS                                        | 103060 | NM_001126 | 1cen-q12     |
|  |                         |                                     | adenylosuccinate lyase/ADSL                                           | 103050 | NM_000026 | 22q13.1      |
|  |                         |                                     | sarcoglycan, delta (35kD dystrophin-associated glycoprotein)/SGCD     | 601411 | NM_000337 | 5q33         |
|  |                         |                                     | phospholamban/PLN                                                     | 172405 | NM_002667 | 6q22.1       |
|  |                         |                                     | desmin/DES                                                            | 125660 | NM_001927 | 2q35         |
|  |                         |                                     | cofilin 2 (muscle)/CFL2                                               | 601443 | *****     | Chr. 12      |
|  |                         |                                     | myosin heavy chain 7, cardiac muscle, beta/MYH7                       | 160760 | NM_000257 | 14q12        |
|  |                         |                                     | cardiac myosin binding protein C/MYBPC3                               | 600958 | NM_000256 | 11p11.2      |
|  |                         |                                     | tropomyosin 1 (alpha)/TPM1                                            | 191010 | NM_000366 | 15q22.1      |
|  |                         |                                     | troponin C, slow/TNNC1                                                | 191040 | NM_003280 | 3p21.3-p14.3 |
|  |                         |                                     | troponin I, cardiac/TNNI3                                             | 191044 | NM_000363 | 19q13.4      |
|  |                         |                                     | troponin T2, cardiac/TNNT2                                            | 191045 | NM_000364 | 1q32         |
|  |                         |                                     | elastin (supravalvular aortic stenosis, Williams-Beuren syndrome)/ELN | 130160 | NM_000501 | 7q11.2       |
|  |                         | Cardiac Muscle Function             |                                                                       |        |           |              |
|  |                         | Structural and Contractile Proteins |                                                                       |        |           |              |

|                                                |                                        |                                                                                                                                 |        |           |               |
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| <b>Cardiac Muscle Structure and Metabolism</b> | <b>Sarcoplasmic Reticulum Function</b> | ATPase, Ca++ transporting, cardiac muscle, fast twitch 1/ATP2A1                                                                 | 108730 | M23114    | 16p12         |
|                                                |                                        | ATPase, Ca++ transporting, cardiac muscle, slow twitch 2/ATP2A2                                                                 | 108740 | NM_001681 | 12q23-q24.1   |
|                                                |                                        | ryanodine receptor 2 (cardiac)/RYR2                                                                                             | 180902 | NM_001035 | 1q42.1-q43    |
|                                                |                                        | calsequestrin 2, fast twitch cardiac muscle/CASQ2                                                                               | 114251 | NM_001232 | 1p13.3-p11    |
| <b>Cardiac Muscle Structure and Metabolism</b> | <b>Mitochondrial Function</b>          | mitochondrial tRNA-Leu (UUR)                                                                                                    | 590050 | S55822    | mitochondrial |
|                                                |                                        | tafazzin (cardiomyopathy, dilated 3A (X-linked); endocardial fibroelastosis 2; Barth syndrome/TAZ                               | 300069 | NM_000116 | Xq28          |
|                                                | <b>Receptors</b>                       | focal adhesion kinase/FAK/PTK2 protein tyrosine kinase                                                                          | 600758 | NM_005607 | 8q24-qter     |
|                                                |                                        | sapiens potassium inwardly-rectifying channel, subfamily J, member 3/KCNJ3                                                      | 600681 | NM_000891 | Chr. 17       |
| <b>Cardiac Muscle Structure and Metabolism</b> | <b>Channels</b>                        | G-protein coupled inwardly rectifying potassium channel/GIRK/potassium inwardly-rectifying channel, subfamily J, member 5/KCNJ5 | 601534 | NM_002239 | 2q24.1        |
|                                                |                                        | ATP sensitive potassium inwardly-rectifying channel, subfamily J, member 5/KCNJ5                                                | 600734 | NM_000890 | 11q24         |
|                                                |                                        | v-Ha-ras Harvey rat sarcoma viral oncogene homolog/HRAS                                                                         | 190020 | NM_005343 | 11p15.5       |
|                                                |                                        | v-Ki-ras2 Kirsten rat sarcoma 2 viral oncogene homolog/KRAS2                                                                    | 190070 | NM_004985 | 12p12.1       |
| <b>Cardiac Muscle Structure and Metabolism</b> |                                        | neuroblastoma RAS viral (v-ras) oncogene homolog/NRAS                                                                           | 164790 | NM_002524 | 1p13.2        |
|                                                |                                        | ras-related C3 botulinum toxin substrate 1                                                                                      | 602048 | NM_006908 | Xq26.2-27.2   |
|                                                |                                        | ras-related C3 botulinum toxin substrate 2                                                                                      | 602049 | NM_002872 | 2q12.3-q13.2  |
|                                                |                                        | ras-related C3 botulinum toxin substrate 3                                                                                      | 602050 | NM_002873 | 2q12.3-q13.2  |

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| <b>Response to Mechanical Stress</b> | <b>Signaling</b>             | ras-related C3 botulinum toxin substrate                                              | 602050 | NM_005052 | 17q24-qter  |
|                                      |                              | LIM domain kinase 1/LIMK1                                                             | 601329 | NM_002314 | 7q11.23     |
|                                      |                              | LIM domain kinase 2/LIMK2                                                             | 601988 | NM_005569 | 22q12       |
|                                      |                              | cell division cycle 42 (GTP-binding protein)                                          | 116952 | NM_001791 | 1p36.1      |
|                                      |                              | p21/Cdc42/Rac1-activated kinase 1 (yeast Ste20-related)/PAK1                          | 602590 | NM_002576 | 11q13-q14   |
|                                      |                              | protein kinase C-like 2/PRKCL2/RAK2                                                   | 602549 | NM_006256 | *****       |
|                                      |                              | oligophenin/OPHN3/p21 (CDKN1A)-activated kinase 3/PAK3                                | 300142 | NM_002578 | Xq21.3-q24  |
|                                      |                              | cardiac-specific homeo box/CSX                                                        | 600584 | NM_004387 | 5q34        |
|                                      |                              | GATA-binding protein 4/GATA4                                                          | 600576 | NM_002052 | 8p23.1-p22  |
|                                      |                              | serum response factor (c-fos serum response element-binding transcription factor)/SRF | 600589 | NM_003131 | *****       |
| <b>Response to Mechanical Stress</b> | <b>Transcription Factors</b> | granulocyte-macrophage colony stimulating factor 2/CSF2                               | 138960 | NM_000758 | 5q31.1      |
|                                      |                              | macrophage-specific colony-stimulating factor/CSF1                                    | 120420 | AH005300  | 1p21-p13    |
|                                      |                              | granulocyte colony stimulating factor 3/CSF3                                          | 138970 | NM_000759 | 17q11.2-q12 |
|                                      |                              | erythropoietin/EPO                                                                    | 133170 | NM_000799 | 7q21        |
|                                      |                              |                                                                                       |        |           |             |

|                                                  |                                                                                          |        |           |               |
|--------------------------------------------------|------------------------------------------------------------------------------------------|--------|-----------|---------------|
|                                                  | flt3 ligand/FMS-related tyrosine kinase 3 ligand/FLT3LG                                  | 600007 | U03858    | 19q13.3       |
|                                                  | thrombopoietin (MLV oncogene ligand, megakaryocyte growth and development factor)/THPO   | 600044 | NM_000460 | 3q26.3-q27    |
| <b>Erythropoiesis</b>                            | granulocyte-macrophage colony stimulating factor 2 receptor, alpha, low-affinity/CSF2RA  | 306250 | NM_006140 | Xp22.32       |
|                                                  | granulocyte-macrophage colony stimulating factor 2 receptor, beta/CSF2RB                 | 138981 | U18373    | 22q12.2-q13.1 |
|                                                  | granulocyte-macrophage colony stimulating factor 2 receptor, alpha, Y chromosomal/CSF2RY | 425000 | *****     | Yp11          |
|                                                  | erythropoietin receptor/EPOR                                                             | 133171 | NM_000121 | 19p13.3-p13.2 |
|                                                  | colony stimulating factor 1 receptor/CSFR1                                               | 164770 | U63963    | 5q33.2-q33.3  |
|                                                  | myeloproliferative leukemia virus oncogene/MPL/thrombopoietin receptor/TPOR              | 159530 | NM_005373 | 1p34          |
|                                                  | Janus kinase 2 (a protein tyrosine kinase)/JAK2                                          | 147796 | NM_004972 | 9p24          |
|                                                  | STAM-like protein containing SH3 and ITAM domains 2/STAM2                                | *****  | NM_005843 | *****         |
|                                                  | ribosomal protein S7/RPS7                                                                | 603474 | NM_001011 | 19q13.2       |
|                                                  | signal transducer and activator of transcription 5A/STAT5A                               | 601511 | NM_003152 | 17q11.2       |
| <b>Receptors</b>                                 |                                                                                          |        |           |               |
| <b>Signaling, Transcription, and Translation</b> |                                                                                          |        |           |               |

|                                                 |                                  |                                                                                        |        |           |               |
|-------------------------------------------------|----------------------------------|----------------------------------------------------------------------------------------|--------|-----------|---------------|
| Erythrocyte<br>Production<br>and<br>Maintenance | Factors                          | BCL-X/BCLX                                                                             | 600039 | Z23115    | *****         |
|                                                 |                                  | STAT induced STAT inhibitor 3/SSI-3                                                    | 604176 | NM_003955 | *****         |
|                                                 |                                  | FMS-related tyrosine kinase 3/FLT3                                                     | 136351 | NM_004119 | 13q12         |
|                                                 | Iron Uptake                      | ATP-binding cassette 7 iron transporter/ABCB7                                          | 300135 | NM_004299 | Xq13.1-q13.3  |
|                                                 |                                  | macrophage protein 2/NRAMP2/solute carrier family 11, member 2/SLC11A2                 | 600523 | AB015355  | 12q13         |
|                                                 | Iron<br>Transport<br>and Storage | transferrin/TF                                                                         | 190000 | NM_001063 | 3q21          |
|                                                 |                                  | transferrin receptor (p90, CD71)/TFRC                                                  | 190010 | NM_003234 | 3q29          |
|                                                 |                                  | transferrin receptor 2/TFR2                                                            | *****  | NM_003227 | *****         |
|                                                 |                                  | iron-responsive element-binding protein 1/iron regulatory protein 1 (IRE-BP1/IREB1)    | 147581 | M58511    | Chr.9         |
|                                                 |                                  | iron-responsive element-binding protein 2/iron regulatory protein 2 (IRE-BP2/IREB2)    | 147582 | M58510    | Chr.15        |
|                                                 |                                  | ferritin, light polypeptide/FTL                                                        | 134790 | NM_000146 | 19q13.3-q13.4 |
|                                                 |                                  | ferritin, heavy polypeptide 1/FTH1                                                     | 134770 | NM_002032 | 11q12-q13     |
|                                                 |                                  | aminolevulinate, delta-, synthase 1, nuclear gene encoding mitochondrial protein/ALAS1 | 301300 | NM_000688 | Xp11.21       |

|                        |                             |                                                                                                                           |        |            |               |
|------------------------|-----------------------------|---------------------------------------------------------------------------------------------------------------------------|--------|------------|---------------|
| <b>Heme Metabolism</b> | <b>Heme Synthesis</b>       | aminolevulinate, delta-, synthase 2 (sideroblastic/hypochromic anemia), nuclear gene encoding mitochondrial protein/ALAS2 | 125290 | NM_000032  | 3p21.1        |
|                        |                             | aminolevulinate, delta-, dehydratase/ALAD                                                                                 | 125270 | NM_000031  | 9q34          |
|                        |                             | uroporphyrinogen III synthase (congenital erythropoietic porphyria)/UROS                                                  | 263700 | NM_0000375 | 10q25.2-q26.3 |
|                        |                             | uroporphyrinogen decarboxylase/UROD                                                                                       | 176100 | NM_0000374 | 1p34          |
|                        |                             | porphobilinogen deaminase/PBGD                                                                                            | 176000 | AH002926   | 11q23.3       |
|                        |                             | protoporphyrinogen oxidase, nuclear gene encoding mitochondrial protein/PPOX                                              | 600923 | NM_0000309 | 1q22          |
|                        |                             | coproporphyrinogen oxidase (coproporphyrin, harderoporphyria), nuclear gene encoding mitochondrial protein/CPO            | 121300 | NM_000097  | 3q12          |
|                        |                             | ferrochelatase (protoporphyrin), nuclear gene encoding mitochondrial protein/FECH                                         | 177000 | NM_000140  | 18q21.3       |
|                        | <b>Hemoglobin Synthesis</b> | hemoglobin, alpha 1/HBA1                                                                                                  | 141800 | NM_000517  | 16pter-p13.3  |
|                        |                             | hemoglobin, alpha 2/HBA2                                                                                                  | 141850 | NM_000558  | 16pter-p13.3  |
|                        |                             | hemoglobin, beta/HBB                                                                                                      | 141900 | NM_000518  | 11p15.5       |



|                            |                                                                                 |        |           |                |
|----------------------------|---------------------------------------------------------------------------------|--------|-----------|----------------|
| <b>Heme<br/>Catabolism</b> | serum beta-glycoprotein hemoexin/HPX                                            | 142290 | AH002827  | 11p15.5-p15.4  |
|                            | inducible heme oxygenase (decycling) 1/HMOX1                                    | 141250 | NM_002133 | 22q12          |
|                            | constitutive heme oxygenase (decycling) 2/HMOX2                                 | 141251 | NM_002134 | 16p13.3        |
|                            | phenol and bilirubin UDP-glucuronosyltransferase/UDP glycosyltransferase 1/UGT1 | 191740 | NM_001072 | Chr.2          |
|                            | UDP glycosyltransferase 2 family, polypeptide B4/UGT2B4                         | 600067 | AF064200  | 4q13           |
|                            | UDP glycosyltransferase 2 family, polypeptide B7/UGT2B7                         | 600068 | NM_001074 | 4q13           |
|                            | biliverdin reductase A/BLVRA                                                    | 109750 | NM_000712 | 7p14-cen       |
|                            | biliverdin reductase B/BLVRB                                                    | 600941 | NM_000713 | 19q13.13-q13.2 |
|                            | ATPase, Ca++ transporting, cardiac muscle, fast twitch 1/ATP2A1                 | 108730 | M23114    | 16p12          |
|                            | ATPase, Ca++ transporting, cardiac muscle, slow twitch 2/ATP2A2                 | 108740 | NM_001681 | 12q23-q24.1    |
| <b>Calcium</b>             | ATPase, Ca++ transporting, ubiquitous/ATP2A3                                    | 601929 | NM_005173 | 17p13.3        |
|                            | ryanodine receptor 3 (brain and smooth muscle)/RYSR3                            | 180903 | NM_001036 | 15q14-q15      |
|                            | calcium channel, voltage-dependent, L type, alpha 1C subunit/CACNA1C            | 114205 | NM_000719 | 12p13.3        |
|                            | potassium voltage-gated channel, shaker-related subfamily, member 4/KCNKA4      | 176266 | NM_002233 | 11q13.4-q14.1  |
|                            |                                                                                 |        |           |                |

|                                      |                  |                                                                                                            |        |           |               |
|--------------------------------------|------------------|------------------------------------------------------------------------------------------------------------|--------|-----------|---------------|
| <b>Cardiac and Vascular Channels</b> | <b>Potassium</b> | potassium voltage-gated channel, Isk-related family, member 1/KCNE1                                        | 176261 | NM_000219 | 21q22.1-q22.2 |
|                                      |                  | potassium voltage-gated channel, Isk-related family, member 2/KCNE2                                        | 603796 | NM_005136 | 21q22.1       |
|                                      |                  | potassium voltage-gated channel, subfamily H, member 2/KCNH2                                               | 152427 | NM_000238 | 7q35-q36      |
|                                      |                  | potassium inwardly-rectifying channel, subfamily J, member 5/KCNJ5                                         | 600734 | NM_000890 | 11q24         |
|                                      |                  | potassium voltage-gated channel precursor, KQT-like subfamily, member 1/KCNQ1                              | 192500 | NM_000218 | 11p15.5       |
|                                      | <b>Sodium</b>    | sodium channel, nonvoltage-gated 1 alpha/SCNN1A                                                            | 600228 | NM_001038 | 12p13         |
|                                      |                  | sodium channel, nonvoltage-gated 1, beta (Liddle syndrome)/SCNN1B                                          | 600760 | NM_000336 | 16p13-p12     |
|                                      |                  | sodium channel, nonvoltage-gated 1, gamma/SCNN1G                                                           | 600761 | NM_001039 | 16p13-p12     |
|                                      |                  | sodium channel, voltage-gated, type V, alpha polypeptide (long (electrocardiographic) QT syndrome 3)/SCN5A | 600163 | NM_000335 | 3p24-p21      |
|                                      |                  | cystic fibrosis transmembrane conductance regulator/CFTR/ATP-binding cassette, subfamily C, member 7/ABCC7 | 602421 | NM_000492 | 7q31.2        |
|                                      | <b>Chloride</b>  | chloride channel, calcium activated, family member 2/CLCA2                                                 | 604003 | NM_006536 | *****         |
|                                      |                  | H+-ATPase beta 1 subunit/ATP6B1                                                                            | 267300 | AH007312  | 2cen-q13      |

|          |                                                                                             |                                                                 |                |                |               |
|----------|---------------------------------------------------------------------------------------------|-----------------------------------------------------------------|----------------|----------------|---------------|
| Acidosis | solute carrier family 4, sodium bicarbonate cotransporter, member 4/SLC4A4                  | 603345                                                          | NM_003759<br>9 | 4q21           |               |
|          | solute carrier family 4, sodium bicarbonate cotransporter, member 5/SLC4A5                  | 603318                                                          | NM_003788<br>8 | 4q21           |               |
|          | carbonic anhydrase II/CA2                                                                   | 259730                                                          | NM_000067<br>7 | 8q22           |               |
|          | carbonic anhydrase IV/CA4                                                                   | 114760                                                          | NM_000717<br>7 | 17q23          |               |
|          | carbonic anhydrase XII/CA12                                                                 | 603263                                                          | AF051882       | 15q22          |               |
|          | solute carrier family 4, bicarbonate/chloride anion exchanger, member 1/SLC4A1              | 109270                                                          | NM_000342<br>2 | 17q21-q22      |               |
|          | solute carrier family 9, member A1/SLC9A1 (sodium/hydrogen ion)                             | 107310                                                          | M81768         | 1p36.1-p35     |               |
|          | solute carrier family 9, member A2/SLC9A2 (sodium/hydrogen ion)                             | 600530                                                          | NM_003048<br>8 | 2q11.2         |               |
|          | solute carrier family 9, member A3/SLC9A3 (sodium/hydrogen ion)                             | 182307                                                          | *****          | 5p15.3         |               |
|          | solute carrier family 9 (sodium/hydrogen exchanger), isoform 3 regulatory factor 1/SLC9A3R1 |                                                                 | NM_004252<br>2 |                |               |
|          | solute carrier family 9 (sodium/hydrogen exchanger), isoform 3 regulatory factor 2/SLC9A3R2 |                                                                 | NM_004785<br>5 |                |               |
|          | Lithosis                                                                                    | Solute carrier family 13, member 2/SLC13A2 (dicarboxylic acids) | 604148         | NM_003984<br>4 | 17p11.1-q11.1 |

Ion and Water Transport

# Renal Channels

|                     |                                                                                     |        |           |               |
|---------------------|-------------------------------------------------------------------------------------|--------|-----------|---------------|
| Urine Concentration | chloride channel 5/CLCN5                                                            | 300008 | NM_000084 | Xp11.22       |
|                     | chloride channel Ka, kidney/CLCNKA                                                  | 602024 | NM_004070 | 1p36          |
|                     | chloride channel Kb, kidney/CLCNKB                                                  | 602023 | NM_000085 | 1p36          |
|                     | solute carrier family 12 (sodium/potassium/chloride transporters), member 1/SLC12A1 | 600839 | NM_000338 | 15q15-q21.1   |
|                     | solute carrier family 12 (sodium/potassium/chloride transporters), member 2/SLC12A2 | 600840 | NM_001046 | 5q23.3        |
|                     | solute carrier family 12 (sodium/chloride transporters), member 2/CLC12A2           | 600968 | NM_000339 | 16q13         |
|                     | ATPase, Na+/K+ transporting, alpha 1 polypeptide/ATP1A1                             | 182310 | NM_000701 | 1p13-p11      |
|                     | ATPase, Na+/K+ transporting, alpha 1 polypeptide-like/ATP1A1L                       | 182360 | NM_001676 | 13q12.1-q12.3 |
|                     | ATPase, Na+/K+ transporting, alpha 2 polypeptide/ATP1A2                             | 182340 | NM_000702 | 1q21-q23      |
|                     | ATPase, Na+/K+ transporting, beta 1 polypeptide/ATP1B1                              | 182330 | NM_001677 | 1q22-q25      |
|                     | ATPase, Na+/K+ transporting, beta 2 polypeptide/ATP1B2                              | 182331 | X16645    | 17p           |
|                     | ATPase, Na+/K+ transporting, beta 3 polypeptide/ATP1B3                              | 601867 | NM_001679 | 3q22-q23      |
|                     | arginine vasopressin receptor 2 (nephrogenic diabetes insipidus 2)                  | 304800 | NM_000054 | Xq28          |
|                     | aquaporin 1/AQP1                                                                    | 107776 | NM_000385 | 7p14          |

|                   |                       |                                                                                                 |        |           |               |
|-------------------|-----------------------|-------------------------------------------------------------------------------------------------|--------|-----------|---------------|
|                   |                       | aquaporin 2/AQP2                                                                                | 107777 | NM_000486 | 12q13         |
|                   |                       | aquaporin 3/AQP3                                                                                | 600170 | NM_004925 | 9p13          |
|                   |                       | aquaporin 6/AQP6                                                                                | 601383 | NM_001652 | 12q13         |
| Vesicle Transport | Cytoskeletal Elements | adducin 1 (alpha subunit)/ADD1                                                                  | 102680 | NM_001119 | 4p16.3        |
|                   |                       | adducin 2 (beta subunit)/ADD2                                                                   | 102681 | AF001597  | 2p14-p13      |
|                   |                       | adducin 3 (gamma subunit)/ADD3                                                                  | 601568 | D67031    | 10q24.2-q24.3 |
| Gap Junctions     | Gap Junctions         | gap junction protein, alpha 1, 43kD (connexin 43)/GJA1                                          | 121014 | NM_000165 | 6q21-q23.2    |
|                   |                       | gap-junction protein alpha 3, 46kD (connexin 46)/GJA3                                           | 121015 | AF075290  | 13q11-q12     |
|                   |                       | gap junction protein, alpha 4, 37kD (connexin 37)/GJA4                                          | 121012 | NM_002060 | 1p35.1        |
|                   |                       | gap junction protein, alpha 5, 40kD (connexin 40)/GJA5                                          | 121013 | NM_005266 | 1q21.1        |
|                   |                       | gap junction protein, alpha 7, 45kD (connexin 45)/GJA7                                          | *****  | NM_005497 | *****         |
|                   |                       | gap junction protein, alpha 8, 50kD (connexin 45)/GJA8                                          | 600897 | NM_005267 | 1q21.1        |
|                   |                       | gap junction protein, beta 1, 32kD (connexin 32, Charcot-Marie-Tooth neuropathy, X-linked)/GJB1 | 304040 | NM_000166 | Xq13.1        |
|                   |                       | gap junction protein, beta 2, 26 kD (connexin 26)/GJB2                                          | 121011 | M86849    | 13q11-q12     |

|  |                                                                                           |        |               |              |
|--|-------------------------------------------------------------------------------------------|--------|---------------|--------------|
|  | gap junction protein, beta 3, 31 kD<br>(connexin 31)/GJB3                                 | 603324 | AF052692      | 1p35.1       |
|  | gap junction protein, beta 5, 31.1 kD<br>(connexin 31.1)/GJB5                             | *****  | AF052693      | *****        |
|  | gap junction protein, beta 6 (connexin<br>30)/GJB6                                        | *****  | NM_00678<br>3 | *****        |
|  | factor I/fibrinogen a, alpha/FGA                                                          | 134820 | NM_000508     | 4q28         |
|  | factor I/fibrinogen b, beta/FGB                                                           | 134830 | AH003492      | 4q28         |
|  | factor I/fibrinogen g, gamma/FGG                                                          | 134850 | NM_000509     | 4q28         |
|  | factor II/prothrombin/F2                                                                  | 176930 | F2            | 11p11-q12    |
|  | coagulation factor II (thrombin)<br>receptor/F2R                                          | 187930 | NM_001992     | 5q13         |
|  | coagulation factor II (thrombin)<br>receptor-like 2/F2RL2                                 | 601919 | NM_004101     | 5q13         |
|  | coagulation factor II (thrombin)<br>receptor-like 3/F2RL3                                 | 602779 | NM_003950     | 19p12        |
|  | tissue factor/factor                                                                      | 134390 | NM_001993     | 1p22-p21     |
|  | tissue factor pathway inhibitor<br>(lipoprotein-associated coagulation<br>inhibitor)/TFPI | 152310 | NM_006287     | 2q31-q32.1   |
|  | tissue factor pathway inhibitor                                                           | 600033 | NM_006528     | 7q22         |
|  | factor V/proaccelerin/labile factor/F5                                                    | 227400 | NM_000130     | 1q23         |
|  | factor VII/serum prothrombin<br>conversion accelerator/F7                                 | 227500 | NM_000131     | 13q34        |
|  | factor VIII/antihemophilic factor/F8                                                      | 306700 | NM_000132     | Xq28         |
|  | factor IX/Christmas factor/plasma<br>thromboplastic component/hemophilia                  | 306900 | NM_000133     | Xq27.1-q27.2 |
|  | factor X/Stuart factor/F10                                                                | 227600 | NM_000504     | 13q34        |
|  | factor XI/plasma thromboplastin<br>antecedent/F11                                         | 264900 | NM_000128     | 4q35         |

brin Formati

Clotting

# Thrombus Formation

|                                                                                                  |        |           |              |
|--------------------------------------------------------------------------------------------------|--------|-----------|--------------|
| factor XII/Hageman factor/F12                                                                    | 234000 | NM_000505 | 5q33-qter    |
| factor XIIIa1/fibrin-stabilizing factor/F13A1                                                    | 134570 | NM_000129 | 6p25-p24     |
| factor XIIIb/fibrin-stabilizing                                                                  | 134580 | *****     | 1q31-q32.1   |
| prekallikrein/Fletcher factor/kallikrein 3, plasma /KLK3                                         | 229000 | NM_000892 | 4q35         |
| kininogen/Flaujeac factor/KNG                                                                    | 228960 | NM_000893 | 3q27         |
| protein S (alpha)/PROS1                                                                          | 176880 | NM_000313 | 3p11.1-q11.2 |
| protein C (inactivator of coagulation factors Va and VIIIa)/PROC                                 | 176860 | NM_000312 | 2q13-q14     |
| antithrombin III/AT3                                                                             |        | NM_000488 | 1q23-q25     |
| gamma-glutamyl carboxylase/GGCX                                                                  | 137167 | NM_000821 | 2p12         |
| plasminogen/PLG                                                                                  | 173350 | NM_000301 | 6q26         |
| monocyte antigen CD87/plasminogen activator receptor, urokinase type/PLAUR/CD87                  | 173391 | NM_002659 | 19q13        |
| plasminogen activator,                                                                           | 191840 | NM_002658 | 10q24        |
| plasminogen activator-tissue/PLAT                                                                | 173370 | A07197    | 8p12         |
| plasminogen activator inhibitor, type I (arginine-serpin)/PAI1                                   | 173360 | X12701    | 7q21.3-q22   |
| plasminogen activator inhibitor, type II (arginine-serpin)/PAI2                                  | 173390 | NM_002575 | 18q21.3      |
| integrin, alpha 2b (platelet glycoprotein IIb of IIb/IIIa complex, antigen CD41B)/ITGA2B         | 273800 | NM_000419 | 17q21.32     |
| integrin beta chain, beta 3 (platelet glycoprotein IIIa of IIb/IIIa complex, antigen CD61)/ITGB3 | 173470 | NM_000212 | 17q21.32     |

## Thrombolysis

|                 |                       |                                                                                                    |        |           |               |
|-----------------|-----------------------|----------------------------------------------------------------------------------------------------|--------|-----------|---------------|
| <b>Adhesion</b> | <b>Clot Adherence</b> | glycoprotein Ib (platelet), alpha polypeptide/GP1BA                                                | 231200 | NM_000173 | 17pter-p12    |
|                 |                       | glycoprotein IX (platelet)/GP9                                                                     | 173515 | NM_000174 | 3q21          |
|                 |                       | calcium and integrin binding protein/CIB                                                           | 602293 | U82226    | 15q25.3-q26   |
|                 |                       | thrombospondin 1/THBS1                                                                             | 188060 | NM_003246 | 15q15         |
|                 |                       | thrombospondin 2/THBS2                                                                             | 188061 | NM_003247 | 6q27          |
|                 |                       | thrombospondin 3/THBS3                                                                             | 188062 | NM_007112 | 1q21          |
|                 |                       | thrombospondin 4/THBS4                                                                             | 600715 | NM_003248 | 5q13          |
|                 |                       | small inducible cytokine subfamily A (Cys-Cys), member 2/monocyte chemotactic protein 1/MCP1/SCYA2 | 158105 | NM_002982 | 17q11.2-q12   |
|                 |                       | macrophage-specific colony-stimulating factor/CSF1                                                 | 120420 | AH005300  | 1p21-p13      |
|                 |                       | interleukin 1 alpha/IL1A                                                                           | 147760 | M15329    | 2q14          |
|                 |                       | interleukin 1 beta/IL1B                                                                            | 147720 | AF043335  | 2q14          |
|                 |                       | apoptosis-related cysteine protease 1/interleukin 1-beta converting enzyme/ICE/caspase 1/CASP1     | 147678 | NM_001223 | 11q22.2-q22.3 |
|                 |                       | interleukin 2/IL2                                                                                  | 147680 | X01586    | 4q26-q27      |
|                 |                       | interleukin 3/IL3                                                                                  | 147740 | NM_000588 | 5q31.1        |
|                 |                       | interleukin 4/IL4                                                                                  | 147780 | NM_000589 | 5q31.1        |



|                                                                                                                 |        |           |               |
|-----------------------------------------------------------------------------------------------------------------|--------|-----------|---------------|
| interleukin 5/IL5                                                                                               | 147850 | NM_000879 | 5q31.1        |
| interleukin 6/IL6                                                                                               | 147620 | AF048692  | 7p21          |
| interleukin 7/IL7                                                                                               | 146660 | NM_000880 | 8q12-q13      |
| interleukin 8/IL8                                                                                               | 146930 | M26383    | 4q12-q13      |
| interleukin 9/IL9                                                                                               | 146931 | X17543    | 5q31.1        |
| interleukin 10/IL10                                                                                             | 124092 | M57627    | 1q31-q32      |
| interleukin 11 beta/IL11B                                                                                       | 147681 | NM_000881 | 19q13.3-q13.4 |
| interleukin 12A (natural killer cell stimulatory factor 1, cytotoxic lymphocyte maturation factor 1, p35)/IL12A | 161560 | NM_002187 | 3p12-q13.2    |
| interleukin 12B/IL12B                                                                                           | 161561 | NM_000440 | 5q31.1-q33.1  |
| interleukin 13/IL13                                                                                             | 147683 | NM_002188 | 5q31          |
| interleukin 15/IL15                                                                                             | 600554 | U14407    | 4q31          |
| interleukin 16/IL16                                                                                             | 603035 | NM_004513 | *****         |
| interleukin 17 (cytotoxic T-lymphocyte-associated serine esterase 3)/IL17                                       | 603149 | NM_002190 | 2q31          |
| interleukin 18 (interferon-gamma-inducing factor)/IL18                                                          | 600953 | NM_001562 | 11q22.2-q22.3 |
| interleukin 1 receptor, type I/IL1R1                                                                            | 147810 | NM_000877 | 2q12          |
| interleukin 1 receptor, type 2/IL1R2                                                                            | 147811 | NM_004633 | 2q12-q22      |

**Cytokines  
and  
Cytokine  
Receptors**

|                                                                    |        |           |               |
|--------------------------------------------------------------------|--------|-----------|---------------|
| interleukin 1 receptor-like 2/IL1RL2                               | *****  | NM_003854 | *****         |
| interleukin 1 receptor accessory protein/IL1RAP                    | 602626 | NM_002182 | 3q28          |
| B-cell antigen CD25/interleukin 2 receptor, alpha chain/IL2RA/CD25 | 147730 | 10p15-p14 | 10p15-p14     |
| interleukin 2 receptor, beta/IL2RB                                 | 146710 | NM_000878 | 22q11.2-q13   |
| interleukin 2 receptor, gamma chain/IL2RG                          | 308380 | NM_000206 | Xq13          |
| interleukin 3 alpha receptor/IL3RA                                 | 308385 | M74782    | Xp22.3        |
| interleukin 4 receptor precursor/IL4R                              | 147781 | NM_000418 | 16p12.1-p11.2 |
| interleukin 5 receptor alpha/IL5RA                                 | 147851 | M96652    | 3p26-p24;     |
| interleukin 6 receptor/IL6R                                        | 147880 | NM_000565 | 1q21          |
| interleukin 7 receptor/IL7R                                        | 146661 | NM_002185 | 5p13          |
| interleukin 9 receptor/IL9R                                        | 300007 | NM_002186 | Xq28          |
| interleukin 10 receptor, alpha/IL10RA                              | 146933 | NM_001558 | 11q23.3       |
| interleukin 10 receptor beta/IL10RB                                | *****  | NM_000628 | *****         |
| interleukin receptor 11 alpha/IL11RA                               | 600939 | NM_004512 | 9p13          |
| interleukin 12 receptor, beta 1/IL12RB1                            | 600939 | NM_005535 | 9p13          |
| interleukin 12 receptor, beta 2/IL12RB2                            | 601642 | NM_001559 | 1p31.2        |

Cell-Mediated Inflammation

|                       |                                                                                     |        |           |           |
|-----------------------|-------------------------------------------------------------------------------------|--------|-----------|-----------|
|                       | interleukin 13 receptor, alpha 1/IL13RA1                                            | 300119 | NM_001560 | Chr.X     |
|                       | interleukin receptor 13 alpha2/IL13A2                                               | 300130 | X95302    | Xq24      |
|                       | interleukin 15 receptor, alpha/IL15RA                                               | 601070 | NM_002189 | 10p15-p14 |
|                       | interleukin 18 receptor 1/IL18R1                                                    | *****  | NM_003855 | *****     |
| Scavenger Receptors   | CD36/thrombospondin receptor/platelet collagen                                      | 173510 | NM_000072 | 7q11.2    |
|                       | CD36 antigen (collagen type I receptor, thrombospondin receptor)-like 1/CD36L1/SRB1 | 601040 | NM_005505 | Chr. 12   |
|                       | CD5 antigen-like (scavenger receptor cysteine rich family)/CD5L                     | 602592 | NM_005894 | 1q21-q23  |
|                       | acetyl LDL receptor/scavenger receptor expressed by endothelial                     | *****  | NM_003693 | *****     |
|                       | macrophage scavenger receptor 1/MSR1                                                | 153622 | NM_002445 | 8p22      |
|                       | macrophage scavenger receptor 1-like/MSRL1                                          | 602728 | *****     | 8p21      |
|                       | macrophage scavenger receptor type III/SRA                                          | 153618 | NM_002438 | 10p13     |
|                       | mannose receptor, C type 1/MRC1                                                     | *****  | NM_006039 | *****     |
|                       | endocytic receptor (macrophage mannose receptor family) (KIAA0709)                  | *****  | NM_006039 | *****     |
|                       | toll-like receptor 1/TLR1                                                           | 601194 | NM_003263 | 4p14      |
|                       | toll-like receptor 2/TLR2                                                           | 603028 | NM_003264 | 4q32      |
|                       | toll-like receptor 3/TLR3                                                           | 603029 | NM_003265 | 4q35      |
|                       | toll-like receptor 4/TLR4                                                           | 603030 | NM_003266 | 9q32-q33  |
|                       | toll-like receptor 5/TLR5                                                           | 603031 | NM_006068 | 1q41-q42  |
|                       |                                                                                     |        |           |           |
|                       |                                                                                     |        |           |           |
| Inflammatory Response |                                                                                     |        |           |           |

|                                              |                                                                                   |        |           |                   |
|----------------------------------------------|-----------------------------------------------------------------------------------|--------|-----------|-------------------|
| (additional<br>genes in<br>Inflammation<br>) | collectin 34                                                                      | *****  | AB002631  | *****             |
|                                              | liver collectin 1/CL-L1                                                           | *****  | NM_006438 | *****             |
|                                              | collectin receptor/complement<br>component C1q receptor/C1QR                      | 120577 | *****     |                   |
|                                              | surfactant, pulmonary-associated<br>protein D/SFTPD                               | 178635 | NM_003019 | 10q23.3           |
|                                              | surfactant, pulmonary-associated<br>protein A1/SFTPA1                             | 178630 | NM_005411 | 10q22.2-q23.1     |
|                                              | myeloperoxidase/MPO                                                               | 254600 | J02694    | 17q23.1           |
|                                              | eosinophil peroxidase/EPX                                                         | 131399 | NM_000502 | *****             |
|                                              | PHOX22/cytochrome b-245, alpha<br>polypeptide/CYBA                                | 233690 | NM_000101 | 16q24             |
|                                              | cytochrome b-245, beta polypeptide<br>(chronic granulomatous<br>disease)/CYBB     | 306400 | NM_000397 | Xp21.1            |
|                                              | PHOX47/soluble oxidase component<br>II/SOC2/neutrophil cytosolic factor<br>1/NCF1 | 233700 | NM_000265 | 7q11.23           |
| Inflammatory<br>Superoxide<br>Generation     | PHOX67/neutrophil cytosolic factor<br>2/NCF2                                      | 233710 | NM_000433 | 1q25              |
|                                              | PHOX40/neutrophil cytosolic factor<br>4/NCF4                                      | 601488 | NM_000631 | 22q13.1           |
|                                              | B-cell antigen CD54/intercellular<br>adhesion molecule 1/ICAM1/CD54               | 147840 | NM_000201 | 19p13.3-<br>p13.2 |
|                                              | receptor for advanced glycation end<br>products/RAGE/AGER                         | 600214 | AJ133822  | 6p21.3            |
| Adhesion                                     | integrin, alpha 7/ITGA7                                                           | 600536 | NM_002206 | 12q13             |
|                                              | integrin, alpha 8/ITGA8                                                           | 604063 | L36531    | *****             |

|                                                                 |        |           |               |
|-----------------------------------------------------------------|--------|-----------|---------------|
| integrin, alpha 9/ITGA9                                         | 603963 | L24158    | 3p21.3        |
| antigen CD29/integrin, beta-1/CD29/ITGB1                        | 135630 | NM_002211 | 10p11.2       |
| vascular cell adhesion molecule 1/VCAM1                         | 192225 | NM_001078 | 1p32-p31      |
| complement component 1, R subcomponent/C1R                      | 216950 | NM_001733 | 12p13         |
| complement component 1, S subcomponent/C1S                      | 120580 | NM_001734 | 12p13         |
| complement component 1, Q subcomponent, alpha polypeptide/C1QA  | 120550 | *****     | 1p36.3-p34.1  |
| complement component 1, Q subcomponent, beta polypeptide/C1QB   | 120570 | *****     | 1p36.3-p34.1  |
| complement component 1, Q subcomponent, gamma polypeptide/C1QG  | 120575 | *****     | 1p36.3-p34.1  |
| complement component 1, Q subcomponent binding protein/C1QBP    | 601269 | NM_001212 | 17p13.3       |
| complement component 1 inhibitor (angioedema, hereditary)/C1INH | 106100 | NM_000062 | 11q11-q13.1   |
| complement component 2/C2                                       | 217000 | NM_000063 | 6p21.3        |
| complement component 3/C3                                       | 120700 | NM_000064 | 19p13.3-p13.2 |
| complement component 4B/C4B                                     | 120820 | NM_000592 | 6p21.3        |
| complement component 5/C5                                       | 120900 | NM_001735 | 9q34.1        |

|                                                                               |        |           |        |
|-------------------------------------------------------------------------------|--------|-----------|--------|
| complement component 6/C6                                                     | 217050 | NM_000065 | 5p13   |
| complement component 7/C7                                                     | 217070 | NM_000587 | 5p13   |
| complement component 8, alpha polypeptide/C8A                                 | 120950 | NM_000562 | 1p32   |
| complement component 8, beta polypeptide/C8B                                  | 120960 | NM_000066 | 1p32   |
| complement component 8, gamma polypeptide/C8G                                 | 120930 | NM_000606 | 9q34.3 |
| complement component 9/C9                                                     | 120940 | NM_001737 | 5p13   |
| complement factor H/H factor 1/HF1                                            | 134370 | NM_000186 | 1q32   |
| I factor (complement)/IF                                                      | 217030 | NM_000204 | 4q25   |
| decay-accelerating factor for complement/DAF/CD55                             | 125240 | S72858    | 1q32   |
| perforin 1/preforming protein/PRF1                                            | 170280 | NM_005041 | 10q22  |
| leukocyte antigen p18-20/protectin/CD59                                       | 107271 | M95708    | 11p13  |
| T-cell antigen CD46/membrane cofactor protein/MCP/measels virus receptor/CD46 | 120920 | Y07713    | 1q32   |
| erythrocyte antigen CD55/decay-accelerating factor for complement/DAF/CD55    | 125240 | S72858    | 1q32   |
| leukocyte antigen p18-20/protectin/CD59                                       | 107271 | M95708    | 11p13  |

### Classical Pathway

### Complement

|                     |                                                                                             |        |           |               |
|---------------------|---------------------------------------------------------------------------------------------|--------|-----------|---------------|
|                     | erythrocyte antigen CD35/complement receptor CR1 (receptor for components C3b/C4b)/CD35/CR1 | 120620 | AH002679  | 1q32          |
|                     | complement component 3a receptor 1/C3AR1                                                    | *****  | NM_004054 | *****         |
|                     | complement component 4-binding protein, alpha/C4BPA                                         | 120830 | NM_000715 | 1q32          |
|                     | complement component 4-binding protein, beta/C4BPB                                          | 120831 | NM_000716 | 1q32          |
|                     | complement component 5 receptor 1 (C5a ligand)/C5AR1                                        | 113995 | NM_001736 | Chr.19        |
|                     | antigen CD21/CD21                                                                           | *****  | X98257    | *****         |
|                     | B-factor, properdin/BF                                                                      | 138470 | NM_001710 | 6p21.3        |
|                     | properdin P factor, complement/PFC                                                          | 312060 | NM_002621 | Xp11.4-p11.23 |
|                     | adipsin/complement factor D precursor/DF                                                    | 134350 | NM_001928 | *****         |
|                     | phospholipase A2 group                                                                      | 172411 | NM_000300 | 1p35          |
| Alternative Pathway | phospholipase A2 group IB/PLA2G1B                                                           | 172410 | NM_000928 | 12q23-q24.1   |
|                     | phospholipase A2 group X/PLA2G10                                                            | 603603 | NM_003561 | 16p13.1-p12   |
|                     | phospholipase A2 group IVA/PLA2G4A                                                          | 600522 | U08374    | 1q25          |
|                     | phospholipase A2 group VI/PLA2G6                                                            | 603604 | AF064594  | 22q13.1       |
|                     | phospholipase A2 group IVC/PLA2G4C                                                          | 603602 | NM_003706 | chr. 19       |
|                     | phospholipase A2 group V/PLA2G5                                                             | 601192 | NM_000929 | 1p36-p34      |
|                     | phospholipase C, beta 2/PLCB2                                                               | 604114 | NM_004573 | 15q15         |
|                     | phospholipase C, beta 3/PLCB3                                                               | 600230 | U26425    | 11q13         |
|                     |                                                                                             |        |           |               |
|                     |                                                                                             |        |           |               |
| Phospholipase       |                                                                                             |        |           |               |

|                                                                                                                      |           |                                                          |        |               |                   |
|----------------------------------------------------------------------------------------------------------------------|-----------|----------------------------------------------------------|--------|---------------|-------------------|
| <b>Release of<br/>Membrane<br/>Lipids</b><br>(common to<br>PAF,<br>leukotriene,<br>and<br>prostaglandin<br>pathways) | <b>es</b> | phospholipase C, beta 4/PLCB4                            | 600810 | NM_000933     | 20p12             |
|                                                                                                                      |           | phospholipase C, delta 1/PLCD1                           | 602142 | NM_006225     | 3p22-p21.3        |
|                                                                                                                      |           | phospholipase C, epsilon/PLCE                            | 600597 | NM_006226     | 2q33              |
|                                                                                                                      |           | phospholipase C, gamma 1 (formerly<br>subtype 148)/PLCG1 | 172420 | NM_002660     | 20q12-q13.1       |
|                                                                                                                      |           | phospholipase C, gamma 2                                 |        |               |                   |
|                                                                                                                      |           | (phosphatidylinositol-specific)/PLCG2                    | 600220 | NM_002661     | 16q24.1           |
|                                                                                                                      |           | phospholipase D1, phosphatidylcholine-<br>specific/PLD1  | 602382 | NM_002662     | 3q26              |
|                                                                                                                      |           | phospholipase D2/PLD2                                    | 602384 | NM_002663     | 17p13.1           |
|                                                                                                                      |           | lysosomal acid lipase/LIPB                               | 278000 | NM_000235     | 10q24-q25         |
|                                                                                                                      |           | lipocortin 1/annexin 1/ANXA1                             | 151690 | V00546        | 9q11-q22          |
| <b>Annexins</b>                                                                                                      |           | lipocortin 2/annexin 2/ANXA2                             | 151740 | D00017        | 15q21-q22         |
|                                                                                                                      |           | lipocortin 3/annexin 3/ANXA3                             | 106490 | M20560        | 4q21              |
|                                                                                                                      |           | lipocortin 5/annexin 5/ANXA4                             | 131230 | NM_00115<br>4 | 4q26-q28          |
|                                                                                                                      |           | lipocortin 7/annexin 7/ANXA1                             | 186360 | NM_00403<br>4 | 10q21.1-<br>q21.2 |
| <b>Arachidonate<br/>Metabolism</b>                                                                                   |           | arachidonate 12-lipoxygenase, 12R<br>type/ALOX12B        | 603741 | NM_00113<br>9 | 17pter-<br>p13.1  |
|                                                                                                                      |           | arachidonate 15-<br>lipoxygenase/ALOX15                  | 152392 | NM_00114<br>0 | 17p13.3           |
|                                                                                                                      |           | arachidonate 15-lipoxygenase, second<br>type/ALOX15B     | 603697 | NM_00114<br>1 | *****             |
|                                                                                                                      |           | prostaglandin endoperoxide synthetase<br>1/COX1/PTGS1    | 176805 | AH001520      | 9q32-q33.3        |
|                                                                                                                      |           | prostaglandin endoperoxide synthetase<br>2/COX2/PTGS2    | 600262 | NM_000963     | 1q25.2-q25.3      |
|                                                                                                                      |           | thromboxane A synthase 1/TBXAS1                          | 274180 | EG_D34613     | 7q34              |



|                                                     |                       |                     |                                                                           |        |           |              |
|-----------------------------------------------------|-----------------------|---------------------|---------------------------------------------------------------------------|--------|-----------|--------------|
| <b>Vasoactive<br/>Mediators of<br/>Inflammation</b> | <b>Prostaglandins</b> | <b>Biosynthesis</b> | prostaglandin D2 synthase<br>(hematopoietic)                              | 602598 | *****     | *****        |
|                                                     |                       |                     | prostaglandin D2 synthase (21kD,<br>brain)/PTGDS                          | 176803 | M61900    | *****        |
|                                                     |                       |                     | prostaglandin I2 synthase/prostacyclin<br>synthase/PTGIS                  | 601699 | EG_D83393 | 20q13        |
|                                                     |                       |                     | prostaglandin E receptor 1, EP1<br>subtype/PTGER1                         | 176802 | NM_000955 | 19p13.1      |
| <b>Prostaglandin<br/>Receptors</b>                  |                       |                     | prostaglandin E receptor 2, EP2<br>subtype/PTGER2                         | 176804 | *****     | 5p13.1       |
|                                                     |                       |                     | prostaglandin E receptor 3, EP3<br>subtype/PTGER3                         | 176806 | NM_000957 | 1p31.2       |
|                                                     |                       |                     | prostaglandin E receptor 4, EP4<br>subtype/PTGER4                         | 601586 | NM_000958 | 5p13.1       |
|                                                     |                       |                     | prostaglandin F receptor/PTGFR                                            | 600563 | L24470    | 1p31.1       |
|                                                     |                       |                     | prostaglandin F2 receptor negative<br>regulator/PTGFRN                    | 601204 | U26664    | 1p13.1-q21.3 |
|                                                     |                       |                     | prostaglandin I2<br>receptor/PTGIR/prostacyclin receptor                  | 600022 | SEG_HUMIF | 19q13.3      |
|                                                     |                       |                     | thromboxane A2 receptor/TBXA2R                                            | 188070 | NM_001060 | 19p13.3      |
|                                                     |                       |                     | solute carrier family 21 (prostaglandin<br>transporter), member 2/SLC21A2 | 601460 | NM_005630 | 3q21         |
|                                                     |                       | <b>Catabolism</b>   | 15-hydroxyprostaglandin<br>dehydrogenase/HPGD                             | 601688 | NM_000860 | 4q34-q35     |
|                                                     |                       |                     | aldo-keto reductase family 1, member<br>C2/AKR1C2                         | 600450 | NM_001353 | 10p15-p14    |
|                                                     |                       |                     | arachidonate 5-lipoxygenase/ALOX5                                         | 152390 | NM_000698 | Chr. 10      |

|                                  |              |                                                                 |        |           |               |
|----------------------------------|--------------|-----------------------------------------------------------------|--------|-----------|---------------|
| Leukotrienes                     | Synthesis    | arachidonate 5-lipoxygenase-activating protein/FLAP/ALOX5AP     | 603700 | NM_001629 | 13q12         |
|                                  |              | leukotriene A4 hydrolase/LTA4H (aminopeptidase)                 | 151570 | NM_000895 | 12q22         |
|                                  |              | leukotriene C4 synthase/LTC4S                                   | 246530 | NM_000897 | 5q35          |
|                                  |              | Gamma-glutamyltranspeptidase 1/GGT1                             | 231950 | J04131    | 22q11.1-q11.2 |
|                                  |              | Gamma-glutamyltranspeptidase 2/GGT2                             | 137181 | AH002728  | 22q11.1       |
|                                  | Receptors    | Gamma-glutamyltransferase-like activity 1/GGTLA1                | 137168 | NM_004121 | *****         |
|                                  |              | cysteinyl leukotriene receptor 1/CYSLT1                         | 300201 | NM_006639 | Xq13-q21      |
|                                  |              | leukotriene b4 receptor (chemokine receptor-like 1)/LTB4R       | 601531 | NM_000752 | 14q11.2-q12   |
|                                  | Catabolism   | renal microsomal dipeptidase/DPEP1                              | 179780 | NM_004413 | 16q24.3       |
|                                  | Biosynthesis | CDP-choline:alkylacetyl glycerol cholinephosphotransferase      | *****  | *****     | *****         |
| Platelet Activating Factor (PAF) | Receptors    | platelet activating factor receptor/PTAFR                       | 173393 | M88177    | 1p35-p34.3    |
|                                  |              | platelet activating factor acetylhydrolase 1/PAFAH1             | 601690 | NM_005084 | 6p21.2-p12    |
|                                  | Catabolism   | platelet activating factor acetylhydrolase, isoform 1B, alpha   | 601545 | NM_000430 | 17p13.3       |
|                                  |              | platelet activating factor acetylhydrolase, isoform 1B, beta    | 602508 | NM_002572 | 11q23         |
|                                  |              | platelet activating factor acetylhydrolase, isoform 1B, gamma   | 603074 | NM_002573 | 19q13.1       |
|                                  |              | platelet activating factor acetylhydrolase, isoform 1B, delta   |        |           |               |
|                                  |              | platelet activating factor acetylhydrolase, isoform 1B, epsilon |        |           |               |
|                                  |              | platelet activating factor acetylhydrolase, isoform 1B, zeta    |        |           |               |
|                                  |              | platelet activating factor acetylhydrolase, isoform 1B, eta     |        |           |               |
|                                  |              | platelet activating factor acetylhydrolase, isoform 1B, theta   |        |           |               |

|                                        |                                                   |                                                   |                                                                                                |        |               |            |
|----------------------------------------|---------------------------------------------------|---------------------------------------------------|------------------------------------------------------------------------------------------------|--------|---------------|------------|
| Amelioration<br>of Oxidative<br>Stress | Antioxidants<br>and Free<br>Radical<br>Scavengers | Antioxidants<br>and Free<br>Radical<br>Scavengers | platelet activating factor<br>acetylhydrolase 2/PAFAH2                                         | 602344 | NM_00043<br>7 | *****      |
|                                        |                                                   |                                                   | superoxide dismutase 1/SOD1                                                                    | 147450 | NM_000454     | 21q22.1    |
|                                        |                                                   |                                                   | superoxide dismutase 2, mitochondrial                                                          | 147460 | X65965        | 6q25.3     |
|                                        |                                                   |                                                   | glutamate-cysteine ligase (gamma-<br>glutamylcysteine synthetase), catalytic<br>(72.8kD)/GLCLC | 230450 | NM_00149<br>8 | 6p12       |
|                                        |                                                   |                                                   | glutathione synthetase/GSS                                                                     | 601002 | NM_00017<br>8 | 20q11.2    |
|                                        |                                                   |                                                   | catalase/CAT                                                                                   | 115500 | NM_001752     | 11p13      |
|                                        |                                                   |                                                   | glutathione peroxidase 1/GPX1                                                                  | 138320 | AF029317      | 3p21.3     |
|                                        |                                                   |                                                   | glutathione peroxidase 2<br>(gastrointestinal)/GPX2                                            | 138319 | NM_00208<br>3 | 14q24.1:   |
|                                        |                                                   |                                                   | glutathione peroxidase 3<br>(plasma)/GPX3                                                      | 138321 | NM_00208<br>4 | 5q32-q33.1 |
|                                        |                                                   |                                                   | glutathione peroxidase 4<br>(phospholipid hydroperoxidase)/GPX4                                | 138322 | NM_00208<br>5 | 19p13.3    |
|                                        | Prevention<br>of Lipid<br>Oxidation               | Prevention<br>of Lipid<br>Oxidation               | glutathione peroxidase 5 (epididymal<br>androgen-related protein)/GPX5                         | 603435 | NM_00150<br>9 | *****      |
|                                        |                                                   |                                                   | ATX1 (antioxidant protein 1, yeast)                                                            | 602270 | NM_00404<br>5 | 5q32-q33   |
|                                        |                                                   |                                                   | homolog 1/ATOX1                                                                                | 152200 | NM_005577     | 6q27       |
|                                        |                                                   |                                                   | apolipoprotein (a), Lp(a)/LPA                                                                  |        |               |            |
|                                        |                                                   |                                                   | paraoxonase 1/PON1 (arylesterase)                                                              | 168820 | NM_00044<br>6 | 7q21.3     |
|                                        |                                                   |                                                   | paraoxonase 2/PON2                                                                             | 602447 | NM_00030<br>5 | 7q21.3     |
|                                        |                                                   |                                                   | paraoxonase 3/PON3                                                                             | 602720 | L48516        | 7q21.4     |
|                                        |                                                   |                                                   | apolipoprotein, Lp(a)/LPA                                                                      | 152200 | NM_00557<br>7 | 6q27       |

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| Table 7. Neurological and Psychiatric Disease Indications |                                | Amyotrophic Lateral Sclerosis | Multiple Sclerosis | Dementia | Parkinson's Disease | Huntington's Disease | Epilepsy | Spasticity |
|-----------------------------------------------------------|--------------------------------|-------------------------------|--------------------|----------|---------------------|----------------------|----------|------------|
| Neuro-transmitters                                        | storage                        |                               |                    |          |                     |                      |          |            |
|                                                           | release                        |                               |                    |          |                     |                      |          |            |
|                                                           | glutamate                      |                               |                    |          |                     |                      |          |            |
|                                                           | serotonin                      |                               |                    |          |                     |                      |          |            |
|                                                           | dopamine                       |                               |                    |          |                     |                      |          |            |
|                                                           | epinephrine and norepinephrine |                               |                    |          |                     |                      |          |            |
|                                                           | acetylcholine                  |                               |                    |          |                     |                      |          |            |
|                                                           | histamine                      |                               |                    |          |                     |                      |          |            |
|                                                           | adenosine                      |                               |                    |          |                     |                      |          |            |
|                                                           | GABA                           |                               |                    |          |                     |                      |          |            |
|                                                           | glycine                        |                               |                    |          |                     |                      |          |            |
|                                                           | taurine                        |                               |                    |          |                     |                      |          |            |
|                                                           | melatonin                      |                               |                    |          |                     |                      |          |            |
|                                                           | nitric oxide                   |                               |                    |          |                     |                      |          |            |
|                                                           | peptide hormone processing     |                               |                    |          |                     |                      |          |            |
|                                                           | opioids                        |                               |                    |          |                     |                      |          |            |
|                                                           | oxytocin                       |                               |                    |          |                     |                      |          |            |
|                                                           | cholecystokinin                |                               |                    |          |                     |                      |          |            |
|                                                           | neuropeptide Y                 |                               |                    |          |                     |                      |          |            |
|                                                           | leptin                         |                               |                    |          |                     |                      |          |            |
|                                                           | neurotensin                    |                               |                    |          |                     |                      |          |            |
|                                                           | tachykinin                     |                               |                    |          |                     |                      |          |            |
|                                                           | bradykinin                     |                               |                    |          |                     |                      |          |            |

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### Table 7. Neurological and Psychiatric Disease Indications

| Table 7. Neurological and Psychiatric Disease Indications |         |            |               |          |                                  |                    |
|-----------------------------------------------------------|---------|------------|---------------|----------|----------------------------------|--------------------|
| Pathway                                                   | Anxiety | Depression | Schizophrenia | Migraine | Ischemic Cerebrovascular Disease | Neuralgia and Pain |
| storage                                                   |         |            |               |          |                                  |                    |
| release                                                   |         |            |               |          |                                  |                    |

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|                                                   |                                        |  |  |  |  |  |  |  |  |
|---------------------------------------------------|----------------------------------------|--|--|--|--|--|--|--|--|
| Cellular Growth, Differentiation, and Maintenance | protein maturation and degradation     |  |  |  |  |  |  |  |  |
|                                                   | second messenger cascade               |  |  |  |  |  |  |  |  |
|                                                   | growth, differentiation, and apoptosis |  |  |  |  |  |  |  |  |
|                                                   | cytoskeleton                           |  |  |  |  |  |  |  |  |
|                                                   | secretion                              |  |  |  |  |  |  |  |  |
|                                                   | adhesion                               |  |  |  |  |  |  |  |  |
|                                                   | amyloid processing                     |  |  |  |  |  |  |  |  |
|                                                   | lipid transport and metabolism         |  |  |  |  |  |  |  |  |
|                                                   | myelination                            |  |  |  |  |  |  |  |  |
|                                                   | folate metabolism                      |  |  |  |  |  |  |  |  |

|                                                   |                                          | Table 8. Toxicological Indication |                 |                    |                   |                  |
|---------------------------------------------------|------------------------------------------|-----------------------------------|-----------------|--------------------|-------------------|------------------|
|                                                   |                                          | Efficacy                          | Safety          |                    |                   |                  |
| Pathway                                           |                                          |                                   | Drug Dyscrasias | Cutaneous Toxicity | Systemic Toxicity | Hepatic Toxicity |
| Absorption and Distribution                       | Gastrointestinal Drug Metabolism         |                                   |                 |                    |                   |                  |
|                                                   | Drug Binding                             |                                   |                 |                    |                   |                  |
|                                                   | Drug Transport                           |                                   |                 |                    |                   |                  |
| Phase I Drug Metabolism (oxidation and reduction) | Monooxygenases (mixed function oxidases) |                                   |                 |                    |                   |                  |
|                                                   | General Oxidases                         |                                   |                 |                    |                   |                  |
|                                                   | Dehydrogenases                           |                                   |                 |                    |                   |                  |
|                                                   | Fatty Acid b-Oxidation                   |                                   |                 |                    |                   |                  |
|                                                   | Reduction                                |                                   |                 |                    |                   |                  |

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| Table 8. Toxicological Indication            |                                                   |                         |                    |                |
|----------------------------------------------|---------------------------------------------------|-------------------------|--------------------|----------------|
|                                              |                                                   | Safety                  |                    |                |
|                                              |                                                   | Cardiovascular Toxicity | Pulmonary Toxicity | Renal Toxicity |
| Absorption and Distribution                  | Gastrointestinal Drug Metabolism                  |                         |                    |                |
|                                              | Drug Binding                                      |                         |                    |                |
|                                              | Drug Transport                                    |                         |                    |                |
|                                              | Monooxygenases ( <i>mixed function oxidases</i> ) |                         |                    |                |
|                                              | General Oxidases                                  |                         |                    |                |
| Phase I Drug Metabolism ( <i>oxidation</i> ) | Dehydrogenases                                    |                         |                    |                |

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|-------------------------------------------------------|---------------------------------------------------|--|--|--|--|--|
| reduction)                                            | Fatty Acid b-Oxidation                            |  |  |  |  |  |
|                                                       | Reduction                                         |  |  |  |  |  |
| Phase II Drug Metabolism (conjugation and catabolism) | Conjugation                                       |  |  |  |  |  |
|                                                       | Catabolism                                        |  |  |  |  |  |
| Excretion                                             | Uptake and Renal Tubular Uptake and Concentration |  |  |  |  |  |
| Organ and Tissue Damage                               | Protection from Radical Damage                    |  |  |  |  |  |
| Immune Response                                       | Mast Cell and T-Cell Response                     |  |  |  |  |  |
|                                                       | B-Cell Response                                   |  |  |  |  |  |
|                                                       | Myeloid Differentiation                           |  |  |  |  |  |

| Table 9. Inflammatory Indication         |                                      |        |                                       |                    |                            |                   |
|------------------------------------------|--------------------------------------|--------|---------------------------------------|--------------------|----------------------------|-------------------|
| Pathway                                  | Arthritis                            | Asthma | Chronic Obstructive Pulmonary Disease | Autoimmune Disease | Inflammatory Bowel Disease | Immunosuppression |
| Immune Discrimination (Self vs Non-Cell) | Antigen Presentation and Recognition |        |                                       |                    |                            |                   |

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### Table 9. Inflammatory Indication

| Pathway                                       | Nephritis | Psoriasis | Atherosclerosis |
|-----------------------------------------------|-----------|-----------|-----------------|
| Antigen Presentation and Recognition          |           |           |                 |
| Interferons, interleukins, TNF Ligand         |           |           |                 |
| Superfamily, Chemokine Superfamily, and other |           |           |                 |
| Chemokine Receptors                           |           |           |                 |
| Cyclophilins                                  |           |           |                 |

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|-------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------|--|--|--|--|
| Cytokine Mediated Immune Regulation | Corticosteroids                                                                                                                            |  |  |  |  |
|                                     | Testosterone/DHT                                                                                                                           |  |  |  |  |
|                                     | Vitamin D                                                                                                                                  |  |  |  |  |
|                                     | Retinoic Acid                                                                                                                              |  |  |  |  |
|                                     | T-Cell, B-Cell, and Myeloid Progenitor Cell Activation, Differentiation, and Proliferation (excluding genes from osteoblast lineage above) |  |  |  |  |
| Cell-Mediated Inflammation          | Apoptosis (additional genes in Oncology)                                                                                                   |  |  |  |  |
|                                     | Adhesion and Migration                                                                                                                     |  |  |  |  |
|                                     | Glycosyltransferases                                                                                                                       |  |  |  |  |
|                                     | Proteases and Protease Inhibitors                                                                                                          |  |  |  |  |
|                                     | Phagocytosis or Pinocytosis                                                                                                                |  |  |  |  |
| Defense Proteins and Peptides       | Immunoglobulin Heavy and Light Chains and Genes Involved in Rearrangement, Isotype Switching, and Transcription                            |  |  |  |  |
|                                     | Complement                                                                                                                                 |  |  |  |  |
|                                     | Acute Protection from Pathogens                                                                                                            |  |  |  |  |

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|                                          |                                                                                        |  |  |  |  |
|------------------------------------------|----------------------------------------------------------------------------------------|--|--|--|--|
| Small Molecule Mediators of Inflammation | Degranulation of Platelets, Mast Cells, Neutrophils, and Eosinophils                   |  |  |  |  |
|                                          | Release of Membrane Lipids<br>(common to PAF, leukotriene, and prostaglandin pathways) |  |  |  |  |
|                                          | Prostaglandins                                                                         |  |  |  |  |
|                                          | Platelet Activating Factor (PAF)                                                       |  |  |  |  |
|                                          | Lipoxins                                                                               |  |  |  |  |
|                                          | Leukotrienes                                                                           |  |  |  |  |
|                                          | Histamine                                                                              |  |  |  |  |
|                                          | Serotonin                                                                              |  |  |  |  |
|                                          | Nitric Oxide Pathway                                                                   |  |  |  |  |
|                                          | Endothelial Growth Factor                                                              |  |  |  |  |
| Vascularization                          | Epinephrine and Norepinephrine Pathway                                                 |  |  |  |  |
| Neurotransmitter and Peptide Hormones    | Dopamine Pathway                                                                       |  |  |  |  |
|                                          | Adenosine Pathway                                                                      |  |  |  |  |
|                                          | Acetylcholine Pathway                                                                  |  |  |  |  |
|                                          | Ion Channels                                                                           |  |  |  |  |
|                                          | Opioids                                                                                |  |  |  |  |
|                                          | Leptin                                                                                 |  |  |  |  |
|                                          | Cholecystokinin (CCK)                                                                  |  |  |  |  |

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|                            |                                                                |  |  |  |  |
|----------------------------|----------------------------------------------------------------|--|--|--|--|
| Inflammatory<br>Modulation | Tachykinin, Substance P,<br>or Neurokinin Pathway              |  |  |  |  |
|                            | Bradykinin                                                     |  |  |  |  |
|                            | Parathyroid Hormone<br>(PTH)                                   |  |  |  |  |
|                            | Melanocortin and<br>Adrenocorticotrophic<br>Hormone            |  |  |  |  |
| General Cell<br>Growth     | Folate Metabolism                                              |  |  |  |  |
|                            | Nucleotide Metabolism                                          |  |  |  |  |
|                            | Cytoskeleton                                                   |  |  |  |  |
|                            | Oxygen Stress<br>( <i>additional genes in<br/>Toxicology</i> ) |  |  |  |  |

| Table 10. Metabolic or Endocrinologic Indication |                                       |                   |                    |         |                |                                         |               |      |
|--------------------------------------------------|---------------------------------------|-------------------|--------------------|---------|----------------|-----------------------------------------|---------------|------|
|                                                  | Pathway                               | Diabetes Mellitus | Diabetes Insipidus | Obesity | Contra-ception | Hormonal Insufficiency Related to Aging | Osteo-porosis | Acne |
| General Metabolism for Peptide Hormones          | Peptide Hormone Processing            |                   |                    |         |                |                                         |               |      |
|                                                  | Peptide Hormone Control of Metabolism |                   |                    |         |                |                                         |               |      |
| Peptide Hormone Control of Metabolism            | Circadian Regulation                  |                   |                    |         |                |                                         |               |      |
|                                                  | Adrenocorticotrophic Hormone          |                   |                    |         |                |                                         |               |      |
|                                                  | Thyroid Hormone                       |                   |                    |         |                |                                         |               |      |
|                                                  | Gonadotropic Hormones                 |                   |                    |         |                |                                         |               |      |

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Table 10. Metabolic or Endocrinologic

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| General Metabolism for Peptide Hormones | Pathway                       | Alopecia | Adrenal Dysfunction | Thyroid Dysfunction | Parathyroid Dysfunction |
|-----------------------------------------|-------------------------------|----------|---------------------|---------------------|-------------------------|
| Peptide Hormone Control of Metabolism   | Peptide Hormone Processing    |          |                     |                     |                         |
|                                         | Circadian Regulation          |          |                     |                     |                         |
|                                         | Adrenocorticotrophic Hormone  |          |                     |                     |                         |
|                                         | Thyroid Hormone               |          |                     |                     |                         |
| Steroid Hormones                        | Gonadotropic Hormones         |          |                     |                     |                         |
|                                         | Progestins                    |          |                     |                     |                         |
|                                         | Estrogens                     |          |                     |                     |                         |
|                                         | Androgens                     |          |                     |                     |                         |
|                                         | Glucocorticoids               |          |                     |                     |                         |
|                                         | Mineralocorticoids            |          |                     |                     |                         |
|                                         | Mediators of Steroid Response |          |                     |                     |                         |
| Neural Regulation of Appetite           | Serotonin                     |          |                     |                     |                         |
|                                         | Dopamine                      |          |                     |                     |                         |
|                                         | Norepinephrine                |          |                     |                     |                         |
| Peptide                                 | Neuropeptide Y                |          |                     |                     |                         |
|                                         | Galanin                       |          |                     |                     |                         |
|                                         | Melanocortin                  |          |                     |                     |                         |
|                                         | Opioids                       |          |                     |                     |                         |
|                                         | Cholecystokinin               |          |                     |                     |                         |

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|                                     |                                  |  |  |  |  |  |
|-------------------------------------|----------------------------------|--|--|--|--|--|
| Hormonal Regulation of Appetite     | Adrenocorticotrophic Hormone     |  |  |  |  |  |
|                                     | PACAP                            |  |  |  |  |  |
|                                     | Enterostatin                     |  |  |  |  |  |
|                                     | Insulin                          |  |  |  |  |  |
|                                     | Leptin                           |  |  |  |  |  |
| Control of Metabolism               | Thyroid Hormone                  |  |  |  |  |  |
|                                     | Glucagon                         |  |  |  |  |  |
|                                     | Glucagon-Like Peptide            |  |  |  |  |  |
| Thermo-regulation                   | Insulin                          |  |  |  |  |  |
|                                     | Uncoupling Proteins              |  |  |  |  |  |
| General Growth Control              | Somatostatin                     |  |  |  |  |  |
|                                     | Growth Hormone                   |  |  |  |  |  |
|                                     | Insulin-Like Growth Factor       |  |  |  |  |  |
|                                     | Fibroblast Growth Factor         |  |  |  |  |  |
|                                     | Sonic Hedgehog                   |  |  |  |  |  |
|                                     | Nerve Growth Factor              |  |  |  |  |  |
|                                     | Neurotrophins                    |  |  |  |  |  |
|                                     | Hormone Signalling               |  |  |  |  |  |
| Carbohydrate Metabolism and Storage | Metabolism                       |  |  |  |  |  |
|                                     | Glycogenic Protein               |  |  |  |  |  |
|                                     | Maturation and                   |  |  |  |  |  |
|                                     | Protein Glycosylation            |  |  |  |  |  |
|                                     | Neovascularization               |  |  |  |  |  |
|                                     | Hemostasis                       |  |  |  |  |  |
|                                     | Amelioration of Oxidative Stress |  |  |  |  |  |

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|                                    |                                   |  |  |  |  |  |
|------------------------------------|-----------------------------------|--|--|--|--|--|
| Adipocyte Differentiation          | Retinoids                         |  |  |  |  |  |
| Lipid Metabolism and Storage       | Peroxisome Proliferation          |  |  |  |  |  |
| Calcium Homeostasis                | Lipid Metabolism and Storage      |  |  |  |  |  |
| Phosphate Homeostasis              | Calcium Metabolism                |  |  |  |  |  |
| Inflammation ( <i>more genes</i> ) | Bone Growth Factors and Receptors |  |  |  |  |  |
|                                    | Vitamin D                         |  |  |  |  |  |
|                                    | Phosphate Metabolism              |  |  |  |  |  |
|                                    | Cytokines                         |  |  |  |  |  |
|                                    | Adhesion                          |  |  |  |  |  |

| Table 11. Cardiovascular or Renal Indication   |                                                                               |        |                 |        |            |              |
|------------------------------------------------|-------------------------------------------------------------------------------|--------|-----------------|--------|------------|--------------|
|                                                | Pathway                                                                       | Anemia | Atherosclerosis | Angina | Arrhythmia | Hypertension |
| Neuroendocrine Control of Heart Rate, Vascular | Dopamine Pathway                                                              |        |                 |        |            |              |
|                                                | Epinephrine and Norepinephrine Pathway                                        |        |                 |        |            |              |
|                                                | Acetylcholine Pathway                                                         |        |                 |        |            |              |
|                                                | Serotonin Pathway                                                             |        |                 |        |            |              |
|                                                | Adenosine Pathway                                                             |        |                 |        |            |              |
|                                                | Histaminergic Pathway                                                         |        |                 |        |            |              |
|                                                | Nitric Oxide Pathway                                                          |        |                 |        |            |              |
|                                                | General Metabolism for Peptide Hormones ( <i>proteases and glycosylases</i> ) |        |                 |        |            |              |
|                                                | Cholecystokinin (CCK)                                                         |        |                 |        |            |              |
|                                                |                                                                               |        |                 |        |            |              |

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Table 11. Cardiovascular or Renal Indication

| Table 11. Cardiovascular or Renal Indication                                  |               |            |               |            |                             |
|-------------------------------------------------------------------------------|---------------|------------|---------------|------------|-----------------------------|
| Pathway                                                                       | Heart Failure | Thrombosis | Renal Disease | Restenosis | Peripheral Vascular Disease |
| Dopamine Pathway                                                              | +             | +          | +             | +          | +                           |
| Epinephrine and Norepinephrine Pathway                                        | +             | +          | +             | +          | +                           |
| Acetylcholine Pathway                                                         | +             | +          | +             | +          | +                           |
| Serotonin Pathway                                                             | +             | +          | +             | +          | +                           |
| Adenosine Pathway                                                             | +             | +          | +             | +          | +                           |
| Histaminergic Pathway                                                         | +             | +          | +             | +          | +                           |
| Nitric Oxide Pathway                                                          | +             | +          | +             | +          | +                           |
| General Metabolism for Peptide Hormones ( <i>proteases and glycosylases</i> ) | +             | +          | +             | +          | +                           |
| Cholecystokinin (CCK)                                                         | +             | +          | +             | +          | +                           |
| Neuropeptide Y (NPY)                                                          | +             | +          | +             | +          | +                           |
| Bradykinin                                                                    | +             | +          | +             | +          | +                           |
| Adrenomedullin                                                                | +             | +          | +             | +          | +                           |
| Angiotensin                                                                   | +             | +          | +             | +          | +                           |

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|--------------------------------------------------|------------------------------------------------------------------------------------------|--|--|--|--|--|--|--|--|
| Cardiac<br>Muscle<br>Structure and<br>Metabolism | Structural and<br>Contractile Proteins                                                   |  |  |  |  |  |  |  |  |
|                                                  | Sarcoplasmic Reticulum<br>Function                                                       |  |  |  |  |  |  |  |  |
|                                                  | Mitochondrial Function                                                                   |  |  |  |  |  |  |  |  |
|                                                  | Response to Mechanical<br>Stress                                                         |  |  |  |  |  |  |  |  |
| Erythrocyte<br>Production                        | Erythropoiesis                                                                           |  |  |  |  |  |  |  |  |
|                                                  | Heme Metabolism                                                                          |  |  |  |  |  |  |  |  |
|                                                  | Cardiac and Vascular<br>Channels                                                         |  |  |  |  |  |  |  |  |
|                                                  | Renal Channels                                                                           |  |  |  |  |  |  |  |  |
| Ion and<br>Water<br>Transport                    | Vesicle Transport                                                                        |  |  |  |  |  |  |  |  |
|                                                  | Gap Junctions                                                                            |  |  |  |  |  |  |  |  |
|                                                  | Clotting                                                                                 |  |  |  |  |  |  |  |  |
|                                                  | Clot Adhesion                                                                            |  |  |  |  |  |  |  |  |
| Inflammatory<br>Response<br>(additional)         | Cell-Mediated<br>Inflammation                                                            |  |  |  |  |  |  |  |  |
|                                                  | Complement                                                                               |  |  |  |  |  |  |  |  |
|                                                  | Release of Membrane<br>Lipids<br>(common to PAF,<br>leukotrienes, and<br>prostaglandins) |  |  |  |  |  |  |  |  |
|                                                  | Vasoactive<br>Mediators of<br>Inflammation                                               |  |  |  |  |  |  |  |  |
|                                                  | Prostaglandins                                                                           |  |  |  |  |  |  |  |  |
|                                                  | Leukotrienes                                                                             |  |  |  |  |  |  |  |  |
|                                                  | Platelet Activating<br>Factor (PAF)                                                      |  |  |  |  |  |  |  |  |
|                                                  |                                                                                          |  |  |  |  |  |  |  |  |

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|                                        |                                             |                                                                                     |                                                                                     |                                                                                    |                                                                                   |                                                                                   |
|----------------------------------------|---------------------------------------------|-------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------|------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------|-----------------------------------------------------------------------------------|
| Amelioration<br>of Oxidative<br>Stress | Antioxidants and Free<br>Radical Scavengers |  |  |  |  |  |
|                                        | Prevention of Lipid<br>Oxidation            |  |  |  |  |  |

Table 12.  
Identified  
Variances  
In Genes  
for  
Pathways  
Identified  
in Cancer  
and  
Related  
Disorders

|          |          |        |             |                                                           |      |         |       |
|----------|----------|--------|-------------|-----------------------------------------------------------|------|---------|-------|
| AB00235  | AB00235  | 603584 | GEN-<br>1CL | Human mRNA for<br>KIAA0358 gene, complete<br>cds          | 269  | 82G>A   | V28M  |
| AB00235  | AB00235  | 603584 | GEN-<br>1CL | Human mRNA for<br>KIAA0358 gene, complete<br>cds          | 1567 | 1380G>A | S     |
| AB00235  | AB00235  | 603584 | GEN-<br>1CL | Human mRNA for<br>KIAA0358 gene, complete<br>cds          | 1627 | 1440C>T | S     |
| AB00235  | AB00235  | 603584 | GEN-<br>1CL | Human mRNA for<br>KIAA0358 gene, complete<br>cds          | 2438 | 2251G>A | V751M |
| AB00714  | AB00714  | 603289 | GEN-13J     | Homo sapiens mRNA for<br>ZIP-kinase, complete cds         | 360  | 267G>T  | S     |
| AB00714  | AB00714  | 603289 | GEN-13J     | Homo sapiens mRNA for<br>ZIP-kinase, complete cds         | 1765 | 1672G>A | 3     |
| AB00787  | AB00787  | 602233 | GEN-104     | Homo sapiens KIAA0413<br>mRNA, complete cds               | 5024 | 5024G>A | 3     |
| AB00787  | AB00787  | 602233 | GEN-104     | Homo sapiens KIAA0413<br>mRNA, complete cds               | 5045 | 5045G>A | 3     |
| AB00787  | AB00787  | 602233 | GEN-104     | Homo sapiens KIAA0413<br>mRNA, complete cds               | 5265 | 5265T>C | 3     |
| AB02068  | AB02068  | None   | GEN-<br>LAX | Homo sapiens mRNA for<br>KIAA0873 protein, partial<br>cds | 3854 | 3854A>G | 3     |
| AF001174 | AF001174 | 602898 | GEN-<br>18T | Homo sapiens p38beta2<br>MAP kinase mRNA,<br>complete cds | 1044 | 1038T>C | S     |
| AF001433 | AF001433 | 601671 | GEN-        | Human requiem (HREQ)                                      | 2378 | 2337T>C | 3     |

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|          |          |        |                    |                                                                                                             |      |         |       |
|----------|----------|--------|--------------------|-------------------------------------------------------------------------------------------------------------|------|---------|-------|
| AF001900 | AF001900 | None   | 18D<br>GEN-<br>17W | mRNA, complete cds<br>Homo sapiens secreted<br>frizzled-related protein                                     | 782  | 480G>C  | S     |
| AF001900 | AF001900 | None   | GEN-<br>17W        | mRNA, complete cds<br>Homo sapiens secreted<br>frizzled-related protein                                     | 1668 | 1366G>A | 3     |
| AF004709 | AF004709 | 602899 | GEN-UX             | mRNA, complete cds<br>Homo sapiens stress-<br>activated protein kinase 4                                    | 432  | 384G>A  | S     |
| AF006689 | AF006689 | 603014 | GEN-YA             | mRNA, complete cds<br>Homo sapiens MAP kinase<br>kinase Jnk2 mRNA,                                          | 75   | (-1)G>A | 5     |
| AF009620 | AF009620 | 601763 | GEN-<br>1HV        | complete cds<br>Homo sapiens apoptotic<br>caspase Mch5-beta<br>mRNA, alternatively<br>spliced, complete cds | 808  | 808C>G  | H270D |
| AF009620 | AF009620 | 601763 | GEN-<br>1HV        | Homo sapiens apoptotic<br>caspase Mch5-beta<br>mRNA, alternatively<br>spliced, complete cds                 | 915  | 915G>A  | S     |
| AF012535 | AF012535 | None   | GEN-<br>1Z2        | spliced, complete cds<br>Homo sapiens death<br>receptor 5 (DR5) mRNA,                                       | 234  | 95T>C   | L32P  |
| AF012535 | AF012535 | None   | GEN-<br>1Z2        | complete cds<br>Homo sapiens death<br>receptor 5 (DR5) mRNA,                                                | 339  | 200C>T  | A67V  |
| AF012535 | AF012535 | None   | GEN-<br>1Z2        | complete cds<br>Homo sapiens death<br>receptor 5 (DR5) mRNA,                                                | 1397 | 1258G>C | 3     |
| AF013988 | AF013988 | 602652 | GEN-<br>20E        | complete cds<br>Homo sapiens serine<br>protease mRNA, complete<br>cds                                       | 271  | 125C>T  | S42L  |
| AF021792 | AF021792 | 603167 | GEN-<br>2A5        | Homo sapiens Bcl-X/Bcl-2<br>binding protein (BAD)<br>mRNA, partial cds                                      | 781  | 781G>A  | 3     |
| AF021792 | AF021792 | 603167 | GEN-<br>2A5        | Homo sapiens Bcl-X/Bcl-2<br>binding protein (BAD)<br>mRNA, partial cds                                      | 883  | 883C>A  | 3     |
| AF026070 | AF026070 | None   | GEN-<br>26S        | Homo sapiens death<br>receptor 3 beta (DR3)                                                                 | 455  | 387A>G  | S     |

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|          |          |        |         |                                                                     |      |         |       |
|----------|----------|--------|---------|---------------------------------------------------------------------|------|---------|-------|
| AF026070 | AF026070 | None   | GEN-26S | mRNA, complete cds                                                  | 1202 | 1134T>C | S     |
|          |          |        |         | Homo sapiens death receptor 3 beta (DR3)                            |      |         |       |
| AF026070 | AF026070 | None   | GEN-26S | mRNA, complete cds                                                  | 1204 | 1136T>G | L379R |
|          |          |        |         | Homo sapiens death receptor 3 beta (DR3)                            |      |         |       |
| AF026070 | AF026070 | None   | GEN-26S | mRNA, complete cds                                                  | 1237 | 1169A>G | H390R |
|          |          |        |         | Homo sapiens death receptor 3 beta (DR3)                            |      |         |       |
| AF027706 | AF027706 | None   | GEN-L9F | mRNA, complete cds                                                  | 1424 | 1200T>A | S     |
|          |          |        |         | Homo sapiens serine/threonine kinase RICK (RICK) mRNA, complete cds |      |         |       |
| AF029761 | AF029761 | None   | GEN-MND | Homo sapiens decoy receptor 2 mRNA, complete cds                    | 1011 | 929C>T  | S310L |
|          |          |        |         | untitled                                                            |      |         |       |
| AF030227 | AF030227 | 164875 | GEN-MM5 |                                                                     | 2702 | 2605G>A | 3     |
|          |          |        |         |                                                                     |      |         |       |
| ITGA7    | AF032108 | 600536 | GEN-2NO | Homo sapiens integrin alpha-7 mRNA, complete cds                    | 527  | 366G>A  | S     |
|          |          |        |         |                                                                     |      |         |       |
| AF035606 | AF035606 | None   | GEN-LCZ | Homo sapiens calcium binding protein (ALG-2) mRNA, complete cds     | 564  | 438C>T  | S     |
|          |          |        |         |                                                                     |      |         |       |
| AF035606 | AF035606 | None   | GEN-LCZ | Homo sapiens calcium binding protein (ALG-2) mRNA, complete cds     | 1006 | 880T>C  | 3     |
|          |          |        |         |                                                                     |      |         |       |
| AF036892 | AF036892 | 601937 | GEN-7W  | Nuclear receptor coactivator (ACTR)                                 | 842  | 659G>T  | R220I |
|          |          |        |         |                                                                     |      |         |       |
| AF036892 | AF036892 | 601937 | GEN-7W  | Nuclear receptor coactivator (ACTR)                                 | 1971 | 1788G>C | Q596H |
|          |          |        |         |                                                                     |      |         |       |
| AF036892 | AF036892 | 601937 | GEN-7W  | Nuclear receptor coactivator (ACTR)                                 | 3048 | 2865A>G | S     |
|          |          |        |         |                                                                     |      |         |       |
| AF036892 | AF036892 | 601937 | GEN-7W  | Nuclear receptor coactivator (ACTR)                                 | 3909 | 3726A>G | S     |
|          |          |        |         |                                                                     |      |         |       |
| AF036892 | AF036892 | 601937 | GEN-7W  | Nuclear receptor coactivator (ACTR)                                 | 4483 | 4300T>C | 3     |
|          |          |        |         |                                                                     |      |         |       |
| AF036892 | AF036892 | 601937 | GEN-7W  | Nuclear receptor coactivator (ACTR)                                 | 5644 | 5461A>G | 3     |
|          |          |        |         |                                                                     |      |         |       |
| AF036892 | AF036892 | 601937 | GEN-7W  | Nuclear receptor coactivator (ACTR)                                 | 5675 | 5492T>A | 3     |
|          |          |        |         |                                                                     |      |         |       |

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|----------|----------|--------|-------------|---------------------------------------------------------------------------------|------|----------|-------|
| AF036892 | AF036892 | 601937 | GEN-7W      | coactivator (ACTR)<br>Nuclear receptor<br>coactivator (ACTR)                    | 6051 | 5868T>G  | 3     |
| AF036892 | AF036892 | 601937 | GEN-7W      | Nuclear receptor<br>coactivator (ACTR)                                          | 6664 | 6481G>A  | 3     |
| AF053712 | AF053712 | None   | GEN-<br>MM2 | Homo sapiens<br>osteoprotegerin ligand<br>mRNA, complete cds                    | 2086 | 1902T>G  | 3     |
| AF093771 | AF093771 | None   | GEN-LTJ     | Homo sapiens<br>mitoxanthrone resistance<br>protein 1 mRNA, partial<br>sequence | 528  | 529G>A   | 3     |
| AJ001838 | AJ001838 | 603758 | GEN-<br>17S | Homo sapiens mRNA for<br>maleylacetoacetate<br>isomerase                        | 65   | (-39)G>C | 5     |
| AJ001838 | AJ001838 | 603758 | GEN-<br>17S | Homo sapiens mRNA for<br>maleylacetoacetate<br>isomerase                        | 197  | 94A>G    | K32E  |
| AJ001838 | AJ001838 | 603758 | GEN-<br>17S | Homo sapiens mRNA for<br>maleylacetoacetate<br>isomerase                        | 227  | 124G>A   | G42R  |
| AJ001838 | AJ001838 | 603758 | GEN-<br>17S | Homo sapiens mRNA for<br>maleylacetoacetate<br>isomerase                        | 348  | 245C>T   | T82M  |
| D00017   | D00017   | 151740 | GEN-2D      | Lipocortin II (Annexin II)                                                      | 149  | 100G>A   | D34N  |
| D00017   | D00017   | 151740 | GEN-2D      | Lipocortin II (Annexin II)                                                      | 341  | 292G>T   | V98L  |
| D00017   | D00017   | 151740 | GEN-2D      | Lipocortin II (Annexin II)                                                      | 479  | 430A>T   | N144Y |
| D00017   | D00017   | 151740 | GEN-2D      | Lipocortin II (Annexin II)                                                      | 1288 | 1239G>A  | 3     |
| D12614   | D12614   | 153440 | GEN-QD      | Human mRNA for<br>lymphotoxin (TNF-beta),<br>complete cds                       | 319  | 179C>A   | T60N  |
| D15057   | D15057   | 600243 | GEN-<br>1T5 | Human mRNA for DAD-1,<br>complete cds                                           | 46   | (-21)C>T | 5     |
| D15057   | D15057   | 600243 | GEN-<br>1T5 | Human mRNA for DAD-1,<br>complete cds                                           | 409  | 343A>C   | 3     |
| D15057   | D15057   | 600243 | GEN-<br>1T5 | Human mRNA for DAD-1,<br>complete cds                                           | 464  | 398G>C   | 3     |
| D15057   | D15057   | 600243 | GEN-<br>1T5 | Human mRNA for DAD-1,<br>complete cds                                           | 500  | 434A>G   | 3     |
| D15057   | D15057   | 600243 | GEN-<br>1T5 | Human mRNA for DAD-1,<br>complete cds                                           | 654  | 588T>C   | 3     |

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|        |        |        |         |                                                    |      |          |        |
|--------|--------|--------|---------|----------------------------------------------------|------|----------|--------|
| D15057 | D15057 | 600243 | GEN-1T5 | complete cds<br>Human mRNA for DAD-1,              | 686  | 620A>C   | 3      |
| D25418 | D25418 | 600022 | GEN-1T5 | complete cds<br>Prostaglandin I2                   | 726  | 635G>A   | R212H  |
| D25418 | D25418 | 600022 | GEN-78  | (prostacyclin) receptor (IP)                       | 1047 | 956C>G   | S319W  |
| D25418 | D25418 | 600022 | GEN-78  | (prostacyclin) receptor (IP)                       | 1075 | 984A>C   | S      |
| D32051 | D32051 | 138440 | GEN-4   | (prostacyclin) receptor (IP)                       | 25   | (-47)G>A | 5      |
| D32051 | D32051 | 138440 | GEN-4   | Glycinamide ribonucleotide<br>transformylase       | 1332 | 1261A>G  | I421V  |
| D32051 | D32051 | 138440 | GEN-4   | Glycinamide ribonucleotide<br>transformylase       | 1855 | 1784G>C  | 3      |
| PTGIR  | D38128 | 600022 | GEN-4DH | Glycinamide ribonucleotide<br>transformylase       | 203  | 204C>G   | 3      |
| PTGIR  | D38128 | 600022 | GEN-4DH | Human IP gene for<br>prostacyclin receptor, exon 3 | 231  | 232C>A   | 3      |
| D38145 | D38145 | 601699 | GEN-4E3 | Human mRNA for<br>prostacyclin synthase,           | 1646 | 1619T>C  | 3      |
| NT5    | D38524 | 129190 | GEN-2PF | complete cds<br>Human mRNA for 5-                  | 3075 | 2992C>T  | 3      |
| D50840 | D50840 | 602874 | GEN-314 | nucleotidase<br>Human mRNA for                     | 638  | 348T>C   | S      |
| D50840 | D50840 | 602874 | GEN-314 | ceramide<br>glucosyltransferase,                   | 1151 | 861A>G   | S      |
| D78586 | D78586 | 114010 | GEN-BR  | complete cds<br>CAD PROTEIN                        | 5308 | 5282C>A  | P1761H |
| D87461 | D87461 | 601931 | GEN-43N | Human mRNA for<br>KIAA0271 gene, complete          | 2432 | 2256C>A  | 3      |
| AAC2   | D90040 | 243400 | GEN-465 | cds<br>Human mRNA for<br>arylamine N-              | 232  | 191G>A   | R64Q   |
|        |        |        |         | acetyltransferase (EC                              |      |          |        |

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| AAC2   | D90040 | 243400 | GEN-465     | Human mRNA for<br>2.3.1.5)<br>arylamine N-<br>acetyltransferase (EC<br>2.3.1.5)                                                        | 323  | 282C>T   | S     |
| AAC2   | D90040 | 243400 | GEN-465     | Human mRNA for<br>2.3.1.5)<br>arylamine N-<br>acetyltransferase (EC<br>2.3.1.5)                                                        | 844  | 803A>G   | K268R |
| D90041 | D90041 | 108345 | GEN-464     | Human liver arylamine N-<br>acetyltransferase (EC<br>2.3.1.5)                                                                          | 591  | 445G>A   | V149I |
| D90041 | D90041 | 108345 | GEN-464     | Human liver arylamine N-<br>acetyltransferase (EC<br>2.3.1.5) gene                                                                     | 1240 | 1094C>A  | 3     |
| DHFR   | J00140 | 126060 | GEN-<br>4E9 | Human dihydrofolate<br>reductase gene                                                                                                  | 721  | 679T>A   | 3     |
| DHFR   | J00140 | 126060 | GEN-<br>4E9 | Human dihydrofolate<br>reductase gene                                                                                                  | 721  | 679T>A   | 3     |
| DHFR   | J00140 | 126060 | GEN-<br>4E9 | Human dihydrofolate<br>reductase gene                                                                                                  | 829  | 787C>T   | 3     |
| J00277 | J00277 | 190020 | GEN-<br>MH8 | Human (genomic clones<br>lambda-[SK2-T2, HS578T];<br>cDNA clones RS-[3.4, 6])<br>c-Ha-ras1 proto-oncogene,<br>complete coding sequence | 81   | 81T>C    | S     |
| J03143 | J03143 | 107470 | GEN-ZK      | Human interferon-gamma<br>receptor mRNA, complete<br>cgs                                                                               | 1098 | 1050T>G  | S     |
| J03209 | J03209 | 185250 | GEN-PK      | Human matrix<br>metalloproteinase-3 (MMP-<br>3) mRNA, complete cds                                                                     | 133  | 133G>A   | E45K  |
| J03209 | J03209 | 185250 | GEN-PK      | Human matrix<br>metalloproteinase-3 (MMP-<br>3) mRNA, complete cds                                                                     | 288  | 288C>T   | S     |
| J03242 | J03242 | 147470 | GEN-PJ      | Insulin-like growth factor 2                                                                                                           | 932  | 380G>A   | R127H |
| J03242 | J03242 | 147470 | GEN-PJ      | Insulin-like growth factor 2                                                                                                           | 1063 | 511G>A   | A171T |
| J03242 | J03242 | 147470 | GEN-PJ      | Insulin-like growth factor 2                                                                                                           | 1190 | 638C>G   | 3     |
| J03242 | J03242 | 147470 | GEN-PJ      | Insulin-like growth factor 2                                                                                                           | 1201 | 649C>T   | 3     |
| J03250 | J03250 | 172420 | GEN-C4      | DNA topoisomerase I                                                                                                                    | 160  | (-52)C>T | 5     |

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|--------|--------|--------|--------|-----------------------------------------------|------|----------------|-------|
| J03250 | J03250 | 172420 | GEN-C4 | DNA topoisomerase I                           | 590  | 379G>A         | V127I |
| J03250 | J03250 | 172420 | GEN-C4 | DNA topoisomerase I                           | 1984 | 1773G>A        | S     |
| J03258 | J03258 | 601769 | GEN-2J | Vitamin D (1,25-dihydroxyvitamin D3) receptor | 172  | 57C>T          | S     |
| J03258 | J03258 | 601769 | GEN-2J | Vitamin D (1,25-dihydroxyvitamin D3) receptor | 559  | 444C>T         | S     |
| J03258 | J03258 | 601769 | GEN-2J | Vitamin D (1,25-dihydroxyvitamin D3) receptor | 1704 | 1589C>A        | 3     |
| J03258 | J03258 | 601769 | GEN-2J | Vitamin D (1,25-dihydroxyvitamin D3) receptor | 1833 | 1718C>G        | 3     |
| J03258 | J03258 | 601769 | GEN-2J | Vitamin D (1,25-dihydroxyvitamin D3) receptor | 1959 | 1844A>C        | 3     |
| J03258 | J03258 | 601769 | GEN-2J | Vitamin D (1,25-dihydroxyvitamin D3) receptor | 3301 | 3186C>A        | 3     |
| J03258 | J03258 | 601769 | GEN-2J | Vitamin D (1,25-dihydroxyvitamin D3) receptor | 3991 | 3876A>G        | 3     |
| J03258 | J03258 | 601769 | GEN-2J | Vitamin D (1,25-dihydroxyvitamin D3) receptor | 4187 | 4072G>A        | 3     |
| J03258 | J03258 | 601769 | GEN-2J | Vitamin D (1,25-dihydroxyvitamin D3) receptor | 4187 | 4072G>A        | 3     |
| J03571 | J03571 | 152390 | GEN-9  | Lipoxygenases: 5-lipoxygenase (leukocytes)    | 55   | 21C>T          | S     |
| J03571 | J03571 | 152390 | GEN-9  | Lipoxygenases: 5-lipoxygenase (leukocytes)    | 304  | 270G>A         | S     |
| J03571 | J03571 | 152390 | GEN-9  | Lipoxygenases: 5-lipoxygenase (leukocytes)    | 304  | 270G>A         | S     |
| J03571 | J03571 | 152390 | GEN-9  | Lipoxygenases: 5-lipoxygenase (leukocytes)    | 959  | 925C>A         | P309T |
| J03571 | J03571 | 152390 | GEN-9  | Lipoxygenases: 5-lipoxygenase (leukocytes)    | 1762 | 1728A>T        | S     |
| J03571 | J03571 | 152390 | GEN-9  | Lipoxygenases: 5-lipoxygenase (leukocytes)    | 2076 | 2042-2043AC>AC | 3     |

|        |        |        |         |                                                                                                     |      |                |       |
|--------|--------|--------|---------|-----------------------------------------------------------------------------------------------------|------|----------------|-------|
| J03571 | J03571 | 152390 | GEN-9   | Lipoxygenases: 5-lipoxygenase (leukocytes)                                                          | 2076 | 2042-2043delAC | F     |
| J03571 | J03571 | 152390 | GEN-9   | Lipoxygenases: 5-lipoxygenase (leukocytes)                                                          | 2328 | 2294C>T        | 3     |
| J03571 | J03571 | 152390 | GEN-9   | Lipoxygenases: 5-lipoxygenase (leukocytes)                                                          | 2376 | 2342T>G        | 3     |
| J03626 | J03626 | 258900 | GEN-C6  | Uridine monophosphate synthetase (orotate phosphoribosyl transferase and orotidine-5-decarboxylase) | 742  | 638G>C         | G213A |
| J03626 | J03626 | 258900 | GEN-C6  | Uridine monophosphate synthetase (orotate phosphoribosyl transferase and orotidine-5-decarboxylase) | 742  | 638G>C         | G213A |
| J03626 | J03626 | 258900 | GEN-C6  | Uridine monophosphate synthetase (orotate phosphoribosyl transferase and orotidine-5-decarboxylase) | 1424 | 1320C>T        | S     |
| J03626 | J03626 | 258900 | GEN-C6  | Uridine monophosphate synthetase (orotate phosphoribosyl transferase and orotidine-5-decarboxylase) | 1575 | 1471A>G        | 3     |
| J03626 | J03626 | 258900 | GEN-C6  | Uridine monophosphate synthetase (orotate phosphoribosyl transferase and orotidine-5-decarboxylase) | 1603 | 1499delT       | F     |
| J03746 | J03746 | 138330 | GEN-11Z | Human glutathione S-transferase mRNA, complete cds                                                  | 560  | 487A>G         | 3     |
| J03746 | J03746 | 138330 | GEN-11Z | Human glutathione S-transferase mRNA, complete cds                                                  | 598  | 525T>G         | 3     |
| J03817 | J03817 | 138350 | GEN-9D  | Glutathione S-transferase M1                                                                        | 99   | 84T>C          | S     |
| J03817 | J03817 | 138350 | GEN-9D  | Glutathione S-transferase M1                                                                        | 543  | 528C>T         | S     |

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|--------|--------|--------|---------|-------------------------------------------------------------------|------|---------|--------|
| J03817 | J03817 | 138350 | GEN-9D  | Glutathione S-transferase<br>M1                                   | 643  | 628T>A  | S210T  |
| J03817 | J03817 | 138350 | GEN-9D  | Glutathione S-transferase<br>M1                                   | 728  | 713C>G  | 3      |
| J03817 | J03817 | 138350 | GEN-9D  | Glutathione S-transferase<br>M1                                   | 902  | 887C>T  | 3      |
| J04031 | J04031 | 172460 | GEN-CB  | Methenyltetrahydrofolate<br>cyclohydrolase                        | 454  | 401G>A  | R134K  |
| J04031 | J04031 | 172460 | GEN-CB  | Methenyltetrahydrofolate<br>cyclohydrolase                        | 969  | 916C>G  | Q306E  |
| J04031 | J04031 | 172460 | GEN-CB  | Methenyltetrahydrofolate<br>cyclohydrolase                        | 1614 | 1561T>C | S      |
| J04031 | J04031 | 172460 | GEN-CB  | Methenyltetrahydrofolate<br>cyclohydrolase                        | 2011 | 1958G>A | R653Q  |
| J04031 | J04031 | 172460 | GEN-CB  | Methenyltetrahydrofolate<br>cyclohydrolase                        | 2335 | 2282C>T | T761M  |
| J04088 | J04088 | 126430 | GEN-8C  | Topoisomerase II alpha                                            | 543  | 507G>A  | S      |
| J04088 | J04088 | 126430 | GEN-8C  | Topoisomerase II alpha                                            | 1385 | 1349G>A | R450Q  |
| J04088 | J04088 | 126430 | GEN-8C  | Topoisomerase II alpha                                            | 1474 | 1438A>G | K480E  |
| J04088 | J04088 | 126430 | GEN-8C  | Topoisomerase II alpha                                            | 1496 | 1460G>A | R487K  |
| J04088 | J04088 | 126430 | GEN-8C  | Topoisomerase II alpha                                            | 1517 | 1481G>A | R494Q  |
| J04088 | J04088 | 126430 | GEN-8C  | Topoisomerase II alpha                                            | 1520 | 1484A>G | E495G  |
| J04088 | J04088 | 126430 | GEN-8C  | Topoisomerase II alpha                                            | 1594 | 1558A>T | F      |
| J04088 | J04088 | 126430 | GEN-8C  | Topoisomerase II alpha                                            | 2443 | 2407C>T | P803S  |
| J04088 | J04088 | 126430 | GEN-8C  | Topoisomerase II alpha                                            | 4008 | 3972A>C | S      |
| J04088 | J04088 | 126430 | GEN-8C  | Topoisomerase II alpha                                            | 4446 | 4410T>G | S      |
| J04145 | J04145 | 120980 | GEN-B   | Leukocyte integrin alpha-m                                        | 206  | 206G>A  | R69H   |
| J04145 | J04145 | 120980 | GEN-B   | Leukocyte integrin alpha-m                                        | 1780 | 1780C>T | S      |
| J04145 | J04145 | 120980 | GEN-B   | Leukocyte integrin alpha-m                                        | 2478 | 2478G>A | S      |
| J04145 | J04145 | 120980 | GEN-B   | Leukocyte integrin alpha-m                                        | 2978 | 2978C>A | T993N  |
| J04145 | J04145 | 120980 | GEN-B   | Leukocyte integrin alpha-m                                        | 3415 | 3415C>T | P1139S |
| J04145 | J04145 | 120980 | GEN-B   | Leukocyte integrin alpha-m                                        | 3661 | 3661C>T | 3      |
| J04145 | J04145 | 120980 | GEN-B   | Leukocyte integrin alpha-m                                        | 3804 | 3804A>G | 3      |
| J04145 | J04145 | 120980 | GEN-B   | Leukocyte integrin alpha-m                                        | 4071 | 4071G>A | 3      |
| GSTM3  | J05459 | 138390 | GEN-170 | Human glutathione<br>transferase M3 (GSTM3)<br>mRNA, complete cds | 687  | 670G>A  | V224I  |
| J05594 | J05594 | 601688 | GEN-E   | Prostaglandin 15-OH                                               | 173  | 156A>G  | S      |

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|--------|--------|--------|--------|------------------------------------------|------|---------------|-------|
| J05594 | J05594 | 601688 | GEN-E  | dehydrogenase (PGDH)                     | 913  | 896C>G        | 3     |
| J05594 | J05594 | 601688 | GEN-E  | Prostaglandin 15-OH dehydrogenase (PGDH) | 950  | 933G>A        | 3     |
| J05594 | J05594 | 601688 | GEN-E  | dehydrogenase (PGDH)                     | 1448 | 1431G>A       | 3     |
| J05594 | J05594 | 601688 | GEN-E  | Prostaglandin 15-OH dehydrogenase (PGDH) | 1972 | 1955T>C       | 3     |
| J05594 | J05594 | 601688 | GEN-E  | Prostaglandin 15-OH dehydrogenase (PGDH) | 1972 | 1955T>C       | 3     |
| K02286 | K02286 | 191840 | GEN-SQ | dehydrogenase (PGDH)                     | 260  | 260C>G        | A87G  |
| K02286 | K02286 | 191840 | GEN-SQ | Human urokinase gene, 3 end              | 449  | 449G>C        | +150S |
| K02286 | K02286 | 191840 | GEN-SQ | Human urokinase gene, 3 end              | 887  | 887A>G        | Y296C |
| K02286 | K02286 | 191840 | GEN-SQ | Human urokinase gene, 3 end              | 902  | 902C>A        | P301H |
| K02286 | K02286 | 191840 | GEN-SQ | Human urokinase gene, 3 end              | 905  | 905A>G        | N302S |
| K02581 | K02581 | 188300 | GEN-CI | Thymidine kinase 1                       | 90   | 33C>T         | S     |
| K02581 | K02581 | 188300 | GEN-CI | Thymidine kinase 1                       | 90   | 33C>T         | S     |
| K02581 | K02581 | 188300 | GEN-CI | Thymidine kinase 1                       | 112  | 55G>A         | G19R  |
| K02581 | K02581 | 188300 | GEN-CI | Thymidine kinase 1                       | 279  | 222G>A        | S     |
| K02581 | K02581 | 188300 | GEN-CI | Thymidine kinase 1                       | 282  | 225G>A        | S     |
| K02581 | K02581 | 188300 | GEN-CI | Thymidine kinase 1                       | 313  | 256C>T        | F     |
| K02581 | K02581 | 188300 | GEN-CI | Thymidine kinase 1                       | 329  | 272-278TGGCTG | S     |
| K02581 | K02581 | 188300 | GEN-CI | Thymidine kinase 1                       | 329  | T>TGGCTGT     | F     |
| K02581 | K02581 | 188300 | GEN-CI | Thymidine kinase 1                       | 334  | 277G>T        | V93F  |
| K02581 | K02581 | 188300 | GEN-CI | Thymidine kinase 1                       | 445  | 388A>G        | R130G |
| K02581 | K02581 | 188300 | GEN-CI | Thymidine kinase 1                       | 479  | 422C>T        | P141L |
| K02581 | K02581 | 188300 | GEN-CI | Thymidine kinase 1                       | 487  | 430G>A        | E144K |
| K02581 | K02581 | 188300 | GEN-CI | Thymidine kinase 1                       | 772  | 715A>G        | 3     |
| K02581 | K02581 | 188300 | GEN-CI | Thymidine kinase 1                       | 867  | 810G>A        | 3     |

|        |        |        |            |                                                                                       |      |          |        |
|--------|--------|--------|------------|---------------------------------------------------------------------------------------|------|----------|--------|
| K02581 | K02581 | 188300 | GEN-CI     | Thymidine kinase 1                                                                    | 867  | 810G>A   | 3      |
| K02770 | K02770 | 147720 | GEN-5M     | Interleukin 1, beta                                                                   | 19   | (-68)A>C | 5      |
| K02770 | K02770 | 147720 | GEN-5M     | Interleukin 1, beta                                                                   | 26   | (-61)A>C | 5      |
| K02770 | K02770 | 147720 | GEN-5M     | Interleukin 1, beta                                                                   | 48   | (-39)C>T | 5      |
| K02770 | K02770 | 147720 | GEN-5M     | Interleukin 1, beta                                                                   | 114  | 28G>A    | E10K   |
| K02770 | K02770 | 147720 | GEN-5M     | Interleukin 1, beta                                                                   | 119  | 33G>A    | M11I   |
| L00634 | L00634 | 134635 | GEN-CK     | Farnesyltransferase, CAAX box, alpha                                                  | 182  | 166G>T   | V56L   |
| L00634 | L00634 | 134635 | GEN-CK     | Farnesyltransferase, CAAX box, alpha                                                  | 184  | 168G>A   | S      |
| L01087 | L01087 | 600448 | GEN-CM     | Protein kinase C-theta                                                                | 1940 | 1846C>A  | S      |
| L01087 | L01087 | 600448 | GEN-CM     | Protein kinase C-theta                                                                | 1943 | 1849G>A  | E617K  |
| GSTM5  | L02321 | 138385 | GEN-<br>WO | Human glutathione S-transferase (GSTM5) mRNA, complete cds                            | 1406 | 1349T>C  | 3      |
| L05628 | L05628 | 158343 | GEN-4D9    | Human multidrug resistance-associated protein (MRP) mRNA, complete cds                | 3369 | 3173G>A  | R1058Q |
| L05628 | L05628 | 158343 | GEN-4D9    | Human multidrug resistance-associated protein (MRP) mRNA, complete cds                | 4198 | 4002G>A  | S      |
| TGFB3  | L07594 | 600742 | GEN-1EA    | Human transforming growth factor-beta type III receptor (TGF-beta) mRNA, complete cds | 3966 | 3618G>C  | 3      |
| L07861 | L07861 | 176977 | GEN-D0     | Protein kinase C, delta                                                               | 445  | 387G>A   | S      |
| L07861 | L07861 | 176977 | GEN-D0     | Protein kinase C, delta                                                               | 1835 | 1777G>A  | V593M  |
| L11284 | L11284 | 176872 | GEN-1K8    | Homosapiens ERK activator kinase (MEK1) mRNA                                          | 1763 | 1764T>C  | 3      |
| L11284 | L11284 | 176872 | GEN-1K8    | Homosapiens ERK activator kinase (MEK1) mRNA                                          | 1914 | 1915G>A  | 3      |
| L11285 | L11285 | 601263 | GEN-1K7    | Homosapiens ERK activator kinase (MEK2) mRNA                                          | 252  | 253C>A   | 3      |
| L11285 | L11285 | 601263 | GEN-1K7    | Homosapiens ERK activator kinase (MEK2) mRNA                                          | 276  | 277T>C   | 3      |

|        |        |        |         |                                                          |      |         |      |
|--------|--------|--------|---------|----------------------------------------------------------|------|---------|------|
| L11285 | L11285 | 601263 | GEN-1K7 | Homosapiens ERK activator kinase (MEK2) mRNA             | 537  | 538C>T  | 3    |
| L11285 | L11285 | 601263 | GEN-1K7 | Homosapiens ERK activator kinase (MEK2) mRNA             | 613  | 614G>C  | 3    |
| L11285 | L11285 | 601263 | GEN-1K7 | Homosapiens ERK activator kinase (MEK2) mRNA             | 744  | 745A>C  | 3    |
| L11285 | L11285 | 601263 | GEN-1K7 | Homosapiens ERK activator kinase (MEK2) mRNA             | 1156 | 1157G>T | 3    |
| L11285 | L11285 | 601263 | GEN-1K7 | Homosapiens ERK activator kinase (MEK2) mRNA             | 1311 | 1312C>T | 3    |
| L11285 | L11285 | 601263 | GEN-1K7 | Homosapiens ERK activator kinase (MEK2) mRNA             | 1457 | 1458C>A | 3    |
| L11285 | L11285 | 601263 | GEN-1K7 | Homosapiens ERK activator kinase (MEK2) mRNA             | 1459 | 1460A>C | 3    |
| L12002 | L12002 | 192975 | GEN-I   | Leukocyte integrin alpha-4 mRNA                          | 1208 | 798T>C  | S    |
| L19182 | L19182 | 602867 | GEN-21Z | Human MAC25 mRNA, complete cds                           | 297  | 284G>A  | R95K |
| L22473 | L22473 | 600040 | GEN-L9D | Human Bax alpha mRNA, complete cds                       | 552  | 552G>A  | S    |
| L24470 | L24470 | 600563 | GEN-O   | PROSTAGLANDIN F RECEPTOR                                 | 1422 | 1185T>C | 3    |
| L24470 | L24470 | 600563 | GEN-O   | PROSTAGLANDIN F RECEPTOR                                 | 1490 | 1253C>T | 3    |
| L24470 | L24470 | 600563 | GEN-O   | PROSTAGLANDIN F RECEPTOR                                 | 1517 | 1280A>G | 3    |
| L24470 | L24470 | 600563 | GEN-O   | PROSTAGLANDIN F RECEPTOR                                 | 2244 | 2007A>G | 3    |
| L24470 | L24470 | 600563 | GEN-O   | PROSTAGLANDIN F RECEPTOR                                 | 2299 | 2062A>G | 3    |
| CDA    | L27943 | 123920 | GEN-4E4 | Homo sapiens cytidine deaminase (CDA) mRNA, complete cds | 552  | 435T>C  | S    |
| PTGER2 | L28175 | 601586 | GEN-7C  | Prostaglandin E receptor 2                               | 547  | 159C>T  | S    |



|        |        |        |         |                                                                                             |      |                    |       |
|--------|--------|--------|---------|---------------------------------------------------------------------------------------------|------|--------------------|-------|
| PTGER2 | L28175 | 601586 | GEN-7C  | (subtype EP2), 53kD<br>Prostaglandin E receptor 2                                           | 611  | 223G>A             | V75M  |
| PTGER2 | L28175 | 601586 | GEN-7C  | (subtype EP2), 53kD<br>Prostaglandin E receptor 2                                           | 1725 | 1337A>G            | Q446R |
| L32866 | L32866 | 603352 | GEN-2JC | (subtype EP2), 53kD<br>Human effector cell<br>protease receptor-1 (EPR-1) gene, partial cds | 308  | 306A>G             | 3     |
| L36719 | L36719 | 602315 | GEN-2NE | Homo sapiens MAP kinase<br>kinase 3 (MKK3) mRNA,<br>complete cds                            | 1227 | 890C>A             | T297N |
| L36719 | L36719 | 602315 | GEN-2NE | Homo sapiens MAP kinase<br>kinase 3 (MKK3) mRNA,<br>complete cds                            | 1271 | 934A>G             | K312E |
| GSTT2  | L38503 | 600437 | GEN-2PC | Homo sapiens glutathione<br>S-transferase theta 2<br>(GSTT2) mRNA, complete<br>cds          | 203  | 203C>T             | S68L  |
| GSTT2  | L38503 | 600437 | GEN-2PC | Homo sapiens glutathione<br>S-transferase theta 2<br>(GSTT2) mRNA, complete<br>cds          | 543  | 543C>T             | S     |
| L41690 | L41690 | None   | GEN-2T4 | Homo sapiens TNF<br>receptor-1 associated<br>protein (TRADD) mRNA, 3<br>end of cds          | 399  | 399G>T             | E133D |
| L41690 | L41690 | None   | GEN-2T4 | Homo sapiens TNF<br>receptor-1 associated<br>protein (TRADD) mRNA, 3<br>end of cds          | 417  | 417G>T             | E139D |
| L78207 | L78207 | 600509 | GEN-5Q  | Cell surface receptor for<br>sulfonylureas on<br>pancreatic b cells                         | 4019 | 3981A>G            | S     |
| M10901 | M10901 | 138040 | GEN-2W  | Corticosteroid nuclear<br>receptor b                                                        | 1220 | 1088A>G            | N363S |
| M10901 | M10901 | 138040 | GEN-2W  | Corticosteroid nuclear<br>receptor b                                                        | 2024 | 1892-<br>1893AG>AG | S     |
| M10901 | M10901 | 138040 | GEN-2W  | Corticosteroid nuclear<br>receptor b                                                        | 2024 | 1892-<br>1893delAG | F     |
| M10901 | M10901 | 138040 | GEN-2W  | Corticosteroid nuclear<br>receptor b                                                        | 2054 | 1922A>T            | D641V |

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|        |        |        |         |                                                                                                |      |         |       |
|--------|--------|--------|---------|------------------------------------------------------------------------------------------------|------|---------|-------|
| M10901 | M10901 | 138040 | GEN-2W  | Corticosteroid nuclear receptor b                                                              | 2372 | 2240T>G | I747S |
| M10901 | M10901 | 138040 | GEN-2W  | Corticosteroid nuclear receptor b                                                              | 2391 | 2259A>C | L753F |
| M10901 | M10901 | 138040 | GEN-2W  | Corticosteroid nuclear receptor b                                                              | 2391 | 2259A>T | L753F |
| M11050 | M11050 | 138040 | GEN-7Y  | Glucocorticoid receptor                                                                        | 2166 | 2034C>T | S     |
| M11050 | M11050 | 138040 | GEN-7Y  | Glucocorticoid receptor                                                                        | 3353 | 3221T>G | 3     |
| M11050 | M11050 | 138040 | GEN-7Y  | Glucocorticoid receptor                                                                        | 3398 | 3266T>G | 3     |
| ETS2   | M11922 | 164740 | GEN-1LG | Human Hu-ets-2 gene, homologous to avian erythroblastosis virus transforming gene, partial cds | 54   | 54A>G   | S     |
| M12674 | M12674 | 133430 | GEN-7Z  | Estrogen receptor                                                                              | 1267 | 975C>G  | S     |
| M12783 | M12783 | 190040 | GEN-QF  | Human c-sis/platelet-derived growth factor 2 (SIS/PDGF2) mRNA, complete cds                    | 1896 | 804T>C  | 3     |
| M12783 | M12783 | 190040 | GEN-QF  | Human c-sis/platelet-derived growth factor 2 (SIS/PDGF2) mRNA, complete cds                    | 2148 | 1056T>C | 3     |
| M12783 | M12783 | 190040 | GEN-QF  | Human c-sis/platelet-derived growth factor 2 (SIS/PDGF2) mRNA, complete cds                    | 2250 | 1158G>A | 3     |
| M13194 | M13194 | 126380 | GEN-EA  | DNA EXCISION REPAIR PROTEIN ERCC-1                                                             | 496  | 354C>T  | S     |
| M13194 | M13194 | 126380 | GEN-EA  | DNA EXCISION REPAIR PROTEIN ERCC-1                                                             | 1078 | 936C>T  | 3     |
| M13509 | M13509 | 120353 | GEN-QJ  | Human skin collagenase mRNA, complete cds                                                      | 383  | 315A>G  | S     |
| M13509 | M13509 | 120353 | GEN-QJ  | Human skin collagenase mRNA, complete cds                                                      | 899  | 831G>A  | S     |
| M13509 | M13509 | 120353 | GEN-QJ  | Human skin collagenase mRNA, complete cds                                                      | 1522 | 1454A>G | 3     |
| M13509 | M13509 | 120353 | GEN-QJ  | Human skin collagenase mRNA, complete cds                                                      | 1747 | 1679C>T | 3     |
| BCL2   | M13994 | 151430 | GEN-1Q9 | Human B-cell leukemia/lymphoma 2 (bcl-                                                         | 1744 | 286G>A  | A96T  |

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|        |        |        |         |                                                       |      |                    |       |
|--------|--------|--------|---------|-------------------------------------------------------|------|--------------------|-------|
| M14221 | M14221 | 161565 | GEN-QM  | proteinase mRNA,<br>complete cds                      | 1557 | 1363G>C            | 3     |
| M14221 | M14221 | 161565 | GEN-QM  | Human cathepsin B<br>proteinase mRNA,<br>complete cds | 1585 | 1391C>A            | 3     |
| M14221 | M14221 | 161565 | GEN-QM  | Human cathepsin B<br>proteinase mRNA,<br>complete cds | 1630 | 1436T>C            | 3     |
| M14221 | M14221 | 161565 | GEN-QM  | Human cathepsin B<br>proteinase mRNA,<br>complete cds | 1668 | 1474T>G            | 3     |
| M14221 | M14221 | 161565 | GEN-QM  | Human cathepsin B<br>proteinase mRNA,<br>complete cds | 1712 | 1518C>G            | 3     |
| M14221 | M14221 | 161565 | GEN-QM  | Human cathepsin B<br>proteinase mRNA,<br>complete cds | 1898 | 1704A>G            | 3     |
| ARG1   | M14502 | 207800 | GEN-1RE | Human liver arginase<br>mRNA, complete cds            | 800  | 744C>T             | S     |
| ABL1   | M14752 | 189980 | GEN-1S7 | Human c-abl gene,<br>complete cds                     | 2233 | 1869G>A            | S     |
| ABL1   | M14752 | 189980 | GEN-1S7 | Human c-abl gene,<br>complete cds                     | 3826 | 3462A>G            | 3     |
| M14758 | M14758 | 171050 | GEN-1S6 | P glycoprotein 1                                      | 978  | 554-<br>555TT>GA>G | V185G |
| M14758 | M14758 | 171050 | GEN-1S6 | P glycoprotein 1                                      | 978  | 554-<br>555TT>TT   | S     |
| M14758 | M14758 | 171050 | GEN-1S6 | P glycoprotein 1                                      | 1623 | 1199G>A            | S400N |
| M14758 | M14758 | 171050 | GEN-1S6 | P glycoprotein 1                                      | 3101 | 2677G>A            | A893T |
| M14758 | M14758 | 171050 | GEN-1S6 | P glycoprotein 1                                      | 3101 | 2677G>T            | A893S |
| M14758 | M14758 | 171050 | GEN-1S6 | P glycoprotein 1                                      | 3859 | 3435C>T            | S     |
| M14758 | M14758 | 171050 | GEN-1S6 | P glycoprotein 1                                      | 4460 | 4036A>G            | 3     |

|        |        |        |         |                                                            |      |          |       |
|--------|--------|--------|---------|------------------------------------------------------------|------|----------|-------|
| NGFR   | M14764 | 162010 | GEN-1S8 | Human nerve growth factor receptor mRNA, complete cds      | 2716 | 2603C>T  | 3     |
| NGFR   | M14764 | 162010 | GEN-1S8 | Human nerve growth factor receptor mRNA, complete cds      | 2729 | 2616C>T  | 3     |
| NGFR   | M14764 | 162010 | GEN-1S8 | Human nerve growth factor receptor mRNA, complete cds      | 2912 | 2799G>A  | 3     |
| NGFR   | M14764 | 162010 | GEN-1S8 | Human nerve growth factor receptor mRNA, complete cds      | 3252 | 3139C>G  | 3     |
| M15395 | M15395 | 600065 | GEN-U   | Leukocyte integrin beta-2                                  | 890  | 818G>A   | G273E |
| M15395 | M15395 | 600065 | GEN-U   | Leukocyte integrin beta-2                                  | 978  | 906A>G   | S     |
| M15395 | M15395 | 600065 | GEN-U   | Leukocyte integrin beta-2                                  | 1173 | 1101C>A  | S     |
| M15395 | M15395 | 600065 | GEN-U   | Leukocyte integrin beta-2                                  | 1395 | 1323T>C  | S     |
| M15395 | M15395 | 600065 | GEN-U   | Leukocyte integrin beta-2                                  | 1614 | 1542C>T  | S     |
| M15395 | M15395 | 600065 | GEN-U   | Leukocyte integrin beta-2                                  | 1965 | 1893C>T  | S     |
| M15395 | M15395 | 600065 | GEN-U   | Leukocyte integrin beta-2                                  | 2505 | 2433G>A  | 3     |
| M15395 | M15395 | 600065 | GEN-U   | Leukocyte integrin beta-2                                  | 2505 | 2433G>A  | 3     |
| M15395 | M15395 | 600065 | GEN-U   | Leukocyte integrin beta-2                                  | 2528 | 2456C>A  | 3     |
| M15395 | M15395 | 600065 | GEN-U   | Leukocyte integrin beta-2                                  | 2528 | 2456C>A  | 3     |
| M15395 | M15395 | 600065 | GEN-U   | Leukocyte integrin beta-2                                  | 2553 | 2481G>C  | 3     |
| PCNA   | M15796 | 176740 | GEN-1UE | Human cyclin protein gene, complete cds                    | 1063 | 945C>G   | 3     |
| M15872 | M15872 | 138360 | GEN-QS  | Human glutathione S-transferase 2 (GST) mRNA, complete cds | 16   | (-40)G>A | 5     |
| M15872 | M15872 | 138360 | GEN-QS  | Human glutathione S-transferase 2 (GST) mRNA, complete cds | 54   | (-2)T>C  | 5     |
| M15872 | M15872 | 138360 | GEN-QS  | Human glutathione S-transferase 2 (GST) mRNA, complete cds | 84   | 29T>C    | F10S  |
| M15872 | M15872 | 138360 | GEN-QS  | Human glutathione S-transferase 2 (GST) mRNA, complete cds | 111  | 56C>T    | T19I  |
| M15872 | M15872 | 138360 | GEN-QS  | Human glutathione S-transferase 2 (GST) mRNA, complete cds | 170  | 115G>T   | F     |

|        |        |        |         |                                                                   |      |         |       |
|--------|--------|--------|---------|-------------------------------------------------------------------|------|---------|-------|
| M15872 | M15872 | 138360 | GEN-QS  | mRNA, complete cds                                                | 321  | 266G>A  | R89K  |
|        |        |        |         | Human glutathione S-transferase 2 (GST)                           |      |         |       |
| M15872 | M15872 | 138360 | GEN-QS  | mRNA, complete cds                                                | 376  | 321C>T  | S     |
|        |        |        |         | Human glutathione S-transferase 2 (GST)                           |      |         |       |
| M15872 | M15872 | 138360 | GEN-QS  | mRNA, complete cds                                                | 430  | 375G>A  | S     |
|        |        |        |         | Human glutathione S-transferase 2 (GST)                           |      |         |       |
| M15872 | M15872 | 138360 | GEN-QS  | mRNA, complete cds                                                | 622  | 567C>T  | S     |
|        |        |        |         | Human glutathione S-transferase 2 (GST)                           |      |         |       |
| M15872 | M15872 | 138360 | GEN-QS  | mRNA, complete cds                                                | 684  | 629A>C  | E210A |
|        |        |        |         | Human glutathione S-transferase 2 (GST)                           |      |         |       |
| M15872 | M15872 | 138360 | GEN-QS  | mRNA, complete cds                                                | 701  | 646G>T  | A216S |
|        |        |        |         | Human glutathione S-transferase 2 (GST)                           |      |         |       |
| M15990 | M15990 | 164880 | GEN-1UR | mRNA, complete cds                                                | 3403 | 3196G>A | 3     |
|        |        |        |         | Human c-yes-1 mRNA                                                |      |         |       |
| M15990 | M15990 | 164880 | GEN-1UR | Human c-yes-1 mRNA                                                | 3864 | 3657G>A | 3     |
|        |        |        |         | Human c-yes-1 mRNA                                                |      |         |       |
| M15990 | M15990 | 164880 | GEN-1UR | Human c-yes-1 mRNA                                                | 3969 | 3762A>C | 3     |
|        |        |        |         | Human c-yes-1 mRNA                                                |      |         |       |
| M15990 | M15990 | 164880 | GEN-1UR | Human c-yes-1 mRNA                                                | 4148 | 3941T>C | 3     |
|        |        |        |         | Human c-yes-1 mRNA                                                |      |         |       |
| M16650 | M16650 | 165640 | GEN-EH  | Ornithine decarboxylase 1                                         | 1330 | 1243G>C | E415Q |
|        |        |        |         | Ornithine decarboxylase 1                                         |      |         |       |
| M16650 | M16650 | 165640 | GEN-EH  | Ornithine decarboxylase 1                                         | 1356 | 1269C>T | S     |
|        |        |        |         | Ornithine decarboxylase 1                                         |      |         |       |
| M20132 | M20132 | 313700 | GEN-38  | Androgen receptor (dihydrotestosterone receptor)                  | 995  | 633G>A  | S     |
|        |        |        |         | Androgen receptor (dihydrotestosterone receptor)                  |      |         |       |
| M20132 | M20132 | 313700 | GEN-38  | Androgen receptor (dihydrotestosterone receptor)                  | 1385 | 1023T>C | S     |
|        |        |        |         | Androgen receptor (dihydrotestosterone receptor)                  |      |         |       |
| M20132 | M20132 | 313700 | GEN-38  | Androgen receptor (dihydrotestosterone receptor)                  | 1786 | 1424G>A | G475E |
|        |        |        |         | Androgen receptor (dihydrotestosterone receptor)                  |      |         |       |
| M20137 | M20137 | 147740 | GEN-CCJ | Human interleukin 3 (IL-3) mRNA, complete cds, clone pcD-SR-alpha | 132  | 79C>T   | P27S  |

|        |        |        |         |                                                                                        |      |          |       |
|--------|--------|--------|---------|----------------------------------------------------------------------------------------|------|----------|-------|
| M20566 | M20566 | 147880 | GEN-3A  | Interleukin 6A                                                                         | 3058 | 2621A>T  | 3     |
| M21154 | M21154 | 180980 | GEN-EM  | S-adenosylmethionine<br>decarboxylase 1                                                | 1050 | 802A>G   | I268V |
| M21154 | M21154 | 180980 | GEN-EM  | S-adenosylmethionine<br>decarboxylase 1                                                | 1139 | 891T>G   | S     |
| M24857 | M24857 | 180190 | GEN-80  | Retinoic acid receptor,<br>gamma 1                                                     | 1694 | 1280C>T  | S427L |
| SCYA3  | M25315 | 601395 | GEN-29M | Homo sapiens (clone pAT<br>464) potential<br>lymphokine/cytokine<br>mRNA, complete cds | 32   | (-52)T>C | 5     |
| SCYA3  | M25315 | 601395 | GEN-29M | Homo sapiens (clone pAT<br>464) potential<br>lymphokine/cytokine<br>mRNA, complete cds | 67   | (-17)G>A | 5     |
| SCYA3  | M25315 | 601395 | GEN-29M | Homo sapiens (clone pAT<br>464) potential<br>lymphokine/cytokine<br>mRNA, complete cds | 110  | 27T>C    | S     |
| SCYA3  | M25315 | 601395 | GEN-29M | Homo sapiens (clone pAT<br>464) potential<br>lymphokine/cytokine<br>mRNA, complete cds | 153  | 70T>C    | S24P  |
| SCYA3  | M25315 | 601395 | GEN-29M | Homo sapiens (clone pAT<br>464) potential<br>lymphokine/cytokine<br>mRNA, complete cds | 203  | 120G>A   | S     |
| SCYA3  | M25315 | 601395 | GEN-29M | Homo sapiens (clone pAT<br>464) potential<br>lymphokine/cytokine<br>mRNA, complete cds | 263  | 180C>T   | S     |
| SCYA3  | M25315 | 601395 | GEN-29M | Homo sapiens (clone pAT<br>464) potential<br>lymphokine/cytokine<br>mRNA, complete cds | 264  | 181G>A   | G61S  |
| SCYA3  | M25315 | 601395 | GEN-29M | Homo sapiens (clone pAT<br>464) potential<br>lymphokine/cytokine<br>mRNA, complete cds | 285  | 202C>A   | S     |
| SCYA3  | M25315 | 601395 | GEN-29M | Homo sapiens (clone pAT<br>464) potential<br>lymphokine/cytokine<br>mRNA, complete cds | 288  | 205A>G   | S69G  |

|       |        |        |             |                                                                                        |     |        |      |
|-------|--------|--------|-------------|----------------------------------------------------------------------------------------|-----|--------|------|
| SCYA3 | M25315 | 601395 | GEN-<br>29M | lymphokine/cytokine<br>mRNA, complete cds<br>Homo sapiens (clone pAT<br>464) potential | 291 | 208C>G | R70G |
| SCYA3 | M25315 | 601395 | GEN-<br>29M | lymphokine/cytokine<br>mRNA, complete cds<br>Homo sapiens (clone pAT<br>464) potential | 335 | 252T>C | S    |
| SCYA3 | M25315 | 601395 | GEN-<br>29M | lymphokine/cytokine<br>mRNA, complete cds<br>Homo sapiens (clone pAT<br>464) potential | 341 | 258C>T | S    |
| SCYA3 | M25315 | 601395 | GEN-<br>29M | lymphokine/cytokine<br>mRNA, complete cds<br>Homo sapiens (clone pAT<br>464) potential | 395 | 312G>A | 3    |
| SCYA3 | M25315 | 601395 | GEN-<br>29M | lymphokine/cytokine<br>mRNA, complete cds<br>Homo sapiens (clone pAT<br>464) potential | 452 | 369C>T | 3    |
| SCYA3 | M25315 | 601395 | GEN-<br>29M | lymphokine/cytokine<br>mRNA, complete cds<br>Homo sapiens (clone pAT<br>464) potential | 479 | 396G>A | 3    |
| SCYA3 | M25315 | 601395 | GEN-<br>29M | lymphokine/cytokine<br>mRNA, complete cds<br>Homo sapiens (clone pAT<br>464) potential | 549 | 466G>A | 3    |
| SCYA3 | M25315 | 601395 | GEN-<br>29M | lymphokine/cytokine<br>mRNA, complete cds<br>Homo sapiens (clone pAT<br>464) potential | 561 | 478C>T | 3    |
| SCYA3 | M25315 | 601395 | GEN-<br>29M | lymphokine/cytokine<br>mRNA, complete cds<br>Homo sapiens (clone pAT<br>464) potential | 617 | 534C>G | 3    |
| SCYA3 | M25315 | 601395 | GEN-<br>29M | lymphokine/cytokine<br>mRNA, complete cds<br>Homo sapiens (clone pAT<br>464) potential | 660 | 577A>G | 3    |



|        |        |        |         |                                                                                              |      |         |       |
|--------|--------|--------|---------|----------------------------------------------------------------------------------------------|------|---------|-------|
| M25753 | M25753 | 123836 | GEN-ET  | mRNA, complete cds                                                                           | 167  | 188C>T  | 3     |
| M25753 | M25753 | 123836 | GEN-ET  | Cyclin B1                                                                                    | 1055 | 1056G>A | 3     |
| M26383 | M26383 | 146930 | GEN-3E  | Interleukin 8                                                                                | 259  | 185C>G  | A62G  |
| M26383 | M26383 | 146930 | GEN-3E  | Interleukin 8                                                                                | 1237 | 1163A>T | 3     |
| M26383 | M26383 | 146930 | GEN-3E  | Interleukin 8                                                                                | 1281 | 1207A>G | 3     |
| M27396 | M27396 | 108370 | GEN-EX  | Asparagine Synthase                                                                          | 807  | 629T>A  | V210E |
| M27396 | M27396 | 108370 | GEN-EX  | Asparagine Synthase                                                                          | 1387 | 1209C>G | S     |
| M27492 | M27492 | 147810 | GEN-3F  | INTERLEUKIN 1 RECEPTOR, TYPE I                                                               | 4686 | 4604T>G | 3     |
| M29696 | M29696 | 146661 | GEN-3H  | PRECURSOR                                                                                    |      |         |       |
| M31145 | M31145 | 146730 | GEN-3J  | Interleukin 7 receptor                                                                       | 1088 | 1066G>A | V356I |
| M31145 | M31145 | 146730 | GEN-3J  | Insulin-like growth factor binding protein 1 precursor                                       | 923  | 759A>G  | I253M |
| M31145 | M31145 | 146730 | GEN-3J  | Insulin-like growth factor binding protein 1 precursor                                       | 1048 | 884T>C  | 3     |
| M31145 | M31145 | 146730 | GEN-3J  | Insulin-like growth factor binding protein 1 precursor                                       | 1260 | 1096C>G | 3     |
| M31159 | M31159 | 146732 | GEN-2GD | Human growth hormone-dependent insulin-like growth factor-binding protein mRNA, complete cds | 204  | 95G>C   | G32A  |
| M31159 | M31159 | 146732 | GEN-2GD | Human growth hormone-dependent insulin-like growth factor-binding protein mRNA, complete cds | 2178 | 2069A>T | 3     |
| M32313 | M32313 | 184753 | GEN-5Y  | Steroid 5 alpha reductase 1                                                                  | 1271 | 1241C>T | 3     |
| M32313 | M32313 | 184753 | GEN-5Y  | Steroid 5 alpha reductase 1                                                                  | 1344 | 1314G>A | 3     |
| M32313 | M32313 | 184753 | GEN-5Y  | Steroid 5 alpha reductase 1                                                                  | 1489 | 1459G>A | 3     |
| M32313 | M32313 | 184753 | GEN-5Y  | Steroid 5 alpha reductase 1                                                                  | 1780 | 1750T>C | 3     |
| M32315 | M32315 | 191191 | GEN-3M  | Tumor necrosis factor receptor 2 (75kD)                                                      | 676  | 587T>G  | M196R |
| M32315 | M32315 | 191191 | GEN-3M  | Tumor necrosis factor receptor 2 (75kD)                                                      | 1176 | 1087G>A | A363T |

|        |        |        |         |                                                                                    |      |         |       |
|--------|--------|--------|---------|------------------------------------------------------------------------------------|------|---------|-------|
| M32315 | M32315 | 191191 | GEN-3M  | Tumor necrosis factor receptor 2 (75kD)                                            | 1668 | 1579G>T | 3     |
| M32315 | M32315 | 191191 | GEN-3M  | Tumor necrosis factor receptor 2 (75kD)                                            | 2898 | 2809G>A | 3     |
| M32315 | M32315 | 191191 | GEN-3M  | Tumor necrosis factor receptor 2 (75kD)                                            | 3671 | 3582G>A | 3     |
| VEGF   | M32977 | 192240 | GEN-2JF | Human heparin-binding vascular endothelial growth factor (VEGF) mRNA, complete cds | 50   | (-7)C>T | 5     |
| VEGF   | M32977 | 192240 | GEN-2JF | Human heparin-binding vascular endothelial growth factor (VEGF) mRNA, complete cds | 92   | 36C>T   | S     |
| RB1    | M33647 | 180200 | GEN-2K1 | Human retinoblastoma associated (RB1) mRNA, complete cds                           | 1105 | 1102G>A | V368I |
| M35011 | M35011 | 147561 | GEN-2LV | Human integrin beta-5 subunit mRNA, complete cds                                   | 1448 | 1419C>T | S     |
| M35011 | M35011 | 147561 | GEN-2LV | Human integrin beta-5 subunit mRNA, complete cds                                   | 2778 | 2749A>C | 3     |
| M35011 | M35011 | 147561 | GEN-2LV | Human integrin beta-5 subunit mRNA, complete cds                                   | 2904 | 2875T>C | 3     |
| M35011 | M35011 | 147561 | GEN-2LV | Human integrin beta-5 subunit mRNA, complete cds                                   | 3077 | 3048G>A | 3     |
| M35011 | M35011 | 147561 | GEN-2LV | Human integrin beta-5 subunit mRNA, complete cds                                   | 3095 | 3066T>A | 3     |
| MET    | M35074 | 164860 | GEN-2LU | Human met oncogene mRNA, 3 end                                                     | 60   | 60C>T   | S     |
| MET    | M35074 | 164860 | GEN-2LU | Human met oncogene mRNA, 3 end                                                     | 294  | 294G>A  | S     |
| M35999 | M35999 | 173470 | GEN-Y   | Leukocyte integrin beta-3                                                          | 53   | 35T>C   | V12A  |
| M35999 | M35999 | 173470 | GEN-Y   | Leukocyte integrin beta-3                                                          | 900  | 882T>C  | S     |
| M35999 | M35999 | 173470 | GEN-Y   | Leukocyte integrin beta-3                                                          | 1161 | 1143C>A | S     |
| M35999 | M35999 | 173470 | GEN-Y   | Leukocyte integrin beta-3                                                          | 1161 | 1143C>A | S     |

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|         |        |        |         |                                                             |      |         |       |
|---------|--------|--------|---------|-------------------------------------------------------------|------|---------|-------|
| M35999  | M35999 | 173470 | GEN-Y   | Leukocyte integrin beta-3                                   | 1551 | 1533G>A | S     |
| M35999  | M35999 | 173470 | GEN-Y   | Leukocyte integrin beta-3                                   | 1551 | 1533G>A | S     |
| M35999  | M35999 | 173470 | GEN-Y   | Leukocyte integrin beta-3                                   | 1563 | 1545G>A | S     |
| M35999  | M35999 | 173470 | GEN-Y   | Leukocyte integrin beta-3                                   | 1563 | 1545G>A | S     |
| M35999  | M35999 | 173470 | GEN-Y   | Leukocyte integrin beta-3                                   | 2226 | 2208C>T | S     |
| M35999  | M35999 | 173470 | GEN-Y   | Leukocyte integrin beta-3                                   | 2426 | 2408G>C | 3     |
| M35999  | M35999 | 173470 | GEN-Y   | Leukocyte integrin beta-3                                   | 3056 | 3038C>T | 3     |
| M35999  | M35999 | 173470 | GEN-Y   | Leukocyte integrin beta-3                                   | 3098 | 3080A>G | 3     |
| M35999  | M35999 | 173470 | GEN-Y   | Leukocyte integrin beta-3                                   | 3403 | 3385A>T | 3     |
| M35999  | M35999 | 173470 | GEN-Y   | Leukocyte integrin beta-3                                   | 3927 | 3909C>T | 3     |
| M37825  | M37825 | 165190 | GEN-2OM | Human fibroblast growth factor-5 (FGF-5) mRNA, complete cds | 787  | 648T>G  | S     |
| M54968  | M54968 | 190070 | GEN-35G | Human K-ras oncogene protein mRNA, complete cds             | 711  | 519T>C  | S     |
| M54968  | M54968 | 190070 | GEN-35G | Human K-ras oncogene protein mRNA, complete cds             | 936  | 744G>T  | 3     |
| M54968  | M54968 | 190070 | GEN-35G | Human K-ras oncogene protein mRNA, complete cds             | 1270 | 1078T>C | 3     |
| M54968  | M54968 | 190070 | GEN-35G | Human K-ras oncogene protein mRNA, complete cds             | 3268 | 3076T>G | 3     |
| M54968  | M54968 | 190070 | GEN-35G | Human K-ras oncogene protein mRNA, complete cds             | 4529 | 4337A>C | 3     |
| M54968  | M54968 | 190070 | GEN-35G | Human K-ras oncogene protein mRNA, complete cds             | 4555 | 4363A>G | 3     |
| M54968  | M54968 | 190070 | GEN-35G | Human K-ras oncogene protein mRNA, complete cds             | 4672 | 4480A>C | 3     |
| CSNK2A1 | M55265 | 115440 | GEN-35Y | Human casein kinase II alpha subunit mRNA, complete cds     | 193  | 45T>C   | S     |
| CSNK2A1 | M55265 | 115440 | GEN-35Y | Human casein kinase II alpha subunit mRNA, complete cds     | 1007 | 859A>C  | S287R |

|         |        |        |         |                                                               |      |           |       |
|---------|--------|--------|---------|---------------------------------------------------------------|------|-----------|-------|
| CSNK2A1 | M55265 | 115440 | GEN-35Y | Human casein kinase II<br>alpha subunit mRNA,<br>complete cds | 1180 | 1032G>A   | S     |
| CSNK2A1 | M55265 | 115440 | GEN-35Y | Human casein kinase II<br>alpha subunit mRNA,<br>complete cds | 1199 | 1051A>G   | M351V |
| CSNK2A2 | M55268 | 115442 | GEN-35X | Human casein kinase II<br>alpha subunit mRNA,<br>complete cds | 1532 | 1369C>A   | 3     |
| M59979  | M59979 | 176805 | GEN-Z   | Cyclooxygenase 1 COX1                                         | 644  | 639C>A    | S     |
| M59979  | M59979 | 176805 | GEN-Z   | Cyclooxygenase 1 COX1                                         | 1892 | 1887C>A   | 3     |
| M59979  | M59979 | 176805 | GEN-Z   | Cyclooxygenase 1 COX1                                         | 2030 | 2025G>A   | 3     |
| M60761  | M60761 | 156569 | GEN-FL  | O-6-methylguanine-DNA<br>methyltransferase                    | 174  | 159C>T    | S     |
| M60761  | M60761 | 156569 | GEN-FL  | O-6-methylguanine-DNA<br>methyltransferase                    | 174  | 159C>T    | S     |
| M60761  | M60761 | 156569 | GEN-FL  | O-6-methylguanine-DNA<br>methyltransferase                    | 174  | 159C>T    | S     |
| M60761  | M60761 | 156569 | GEN-FL  | O-6-methylguanine-DNA<br>methyltransferase                    | 210  | 195G>C    | W65C  |
| M60761  | M60761 | 156569 | GEN-FL  | O-6-methylguanine-DNA<br>methyltransferase                    | 264  | 249A>T    | S     |
| M60761  | M60761 | 156569 | GEN-FL  | O-6-methylguanine-DNA<br>methyltransferase                    | 265  | 250C>T    | L84F  |
| M60761  | M60761 | 156569 | GEN-FL  | O-6-methylguanine-DNA<br>methyltransferase                    | 265  | 250C>T    | L84F  |
| M60761  | M60761 | 156569 | GEN-FL  | O-6-methylguanine-DNA<br>methyltransferase                    | 442  | 427A>G    | I143V |
| M60761  | M60761 | 156569 | GEN-FL  | O-6-methylguanine-DNA<br>methyltransferase                    | 442  | 427A>G    | I143V |
| M60761  | M60761 | 156569 | GEN-FL  | O-6-methylguanine-DNA<br>methyltransferase                    | 493  | 478G>A    | G160R |
| M60761  | M60761 | 156569 | GEN-FL  | O-6-methylguanine-DNA<br>methyltransferase                    | 548  | 533A>G    | K178R |
| M60761  | M60761 | 156569 | GEN-FL  | O-6-methylguanine-DNA<br>methyltransferase                    | 582  | 567G>A    | S     |
| FGF7    | M60828 | 148180 | GEN-3BE | Human keratinocyte<br>growth factor mRNA,<br>complete cds     | 323  | (-123)G>C | 5     |
| FGF7    | M60828 | 148180 | GEN-3BE | Human keratinocyte<br>growth factor mRNA,<br>complete cds     | 1180 | 735T>C    | 3     |

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|------|--------|--------|-------------|-----------------------------------------------------------|------|---------|---|
| FGF7 | M60828 | 148180 | GEN-<br>3BE | complete cds<br>Human keratinocyte<br>growth factor mRNA, | 1201 | 756A>G  | 3 |
| FGF7 | M60828 | 148180 | GEN-<br>3BE | complete cds<br>Human keratinocyte<br>growth factor mRNA, | 1216 | 771A>G  | 3 |
| FGF7 | M60828 | 148180 | GEN-<br>3BE | complete cds<br>Human keratinocyte<br>growth factor mRNA, | 1218 | 773G>C  | 3 |
| FGF7 | M60828 | 148180 | GEN-<br>3BE | complete cds<br>Human keratinocyte<br>growth factor mRNA, | 1266 | 821A>C  | 3 |
| FGF7 | M60828 | 148180 | GEN-<br>3BE | complete cds<br>Human keratinocyte<br>growth factor mRNA, | 1306 | 861C>T  | 3 |
| FGF7 | M60828 | 148180 | GEN-<br>3BE | complete cds<br>Human keratinocyte<br>growth factor mRNA, | 1654 | 1209A>T | 3 |
| FGF7 | M60828 | 148180 | GEN-<br>3BE | complete cds<br>Human keratinocyte<br>growth factor mRNA, | 1657 | 1212T>C | 3 |
| FGF7 | M60828 | 148180 | GEN-<br>3BE | complete cds<br>Human keratinocyte<br>growth factor mRNA, | 1799 | 1354A>T | 3 |
| FGF7 | M60828 | 148180 | GEN-<br>3BE | complete cds<br>Human keratinocyte<br>growth factor mRNA, | 1801 | 1356C>T | 3 |
| FGF7 | M60828 | 148180 | GEN-<br>3BE | complete cds<br>Human keratinocyte<br>growth factor mRNA, | 1867 | 1422A>G | 3 |
| FGF7 | M60828 | 148180 | GEN-<br>3BE | complete cds<br>Human keratinocyte<br>growth factor mRNA, | 1945 | 1500C>A | 3 |
| FGF7 | M60828 | 148180 | GEN-<br>3BE | complete cds<br>Human keratinocyte<br>growth factor mRNA, | 1973 | 1528G>A | 3 |
| FGF7 | M60828 | 148180 | GEN-<br>3BE | complete cds<br>Human keratinocyte<br>growth factor mRNA, | 2167 | 1722G>A | 3 |
| FGF7 | M60828 | 148180 | GEN-<br>3BE | complete cds<br>Human keratinocyte<br>growth factor mRNA, | 2186 | 1741A>G | 3 |

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|--------|--------|--------|---------|--------------------------------------------------------------------------------|------|---------|---|
| FGF7   | M60828 | 148180 | 3BE     | growth factor mRNA, complete cds                                               | 2302 | 1857T>A | 3 |
|        |        |        | GEN-3BE | Human keratinocyte growth factor mRNA, complete cds                            | 2328 | 1883G>A | 3 |
| FGF7   | M60828 | 148180 | GEN-3BE | Human keratinocyte growth factor mRNA, complete cds                            | 693  | 669A>G  | S |
| M61764 | M61764 | 191135 | GEN-FO  | Tubulin, gamma polypeptide                                                     | 723  | 699T>C  | S |
| M61764 | M61764 | 191135 | GEN-FO  | Tubulin, gamma polypeptide                                                     | 849  | 825T>G  | S |
| M61764 | M61764 | 191135 | GEN-FO  | Tubulin, gamma polypeptide                                                     | 858  | 834G>A  | S |
| M61764 | M61764 | 191135 | GEN-FO  | Tubulin, gamma polypeptide                                                     | 1033 | 1009T>C | S |
| M61764 | M61764 | 191135 | GEN-FO  | Tubulin, gamma polypeptide                                                     | 1053 | 1029C>G | S |
| M61764 | M61764 | 191135 | GEN-FO  | Tubulin, gamma polypeptide                                                     | 1131 | 1107G>A | S |
| M61764 | M61764 | 191135 | GEN-FO  | Tubulin, gamma polypeptide                                                     | 1188 | 1164C>T | S |
| IGFBP4 | M62403 | 146733 | GEN-3CJ | Human insulin-like growth factor binding protein 4 (IGFBP4) mRNA, complete cds | 859  | 776G>A  | S |
| IGFBP4 | M62403 | 146733 | GEN-3CJ | Human insulin-like growth factor binding protein 4 (IGFBP4) mRNA, complete cds | 1403 | 1320G>T | 3 |
| IGFBP4 | M62403 | 146733 | GEN-3CJ | Human insulin-like growth factor binding protein 4 (IGFBP4) mRNA, complete cds | 1443 | 1360G>A | 3 |
| IGFBP4 | M62403 | 146733 | GEN-3CJ | Human insulin-like growth factor binding protein 4 (IGFBP4) mRNA, complete cds | 1446 | 1363G>A | 3 |
| IGFBP4 | M62403 | 146733 | GEN-3CJ | Human insulin-like growth factor binding protein 4 (IGFBP4) mRNA, complete cds | 1485 | 1402A>T | 3 |

|        |        |        |         |                                                                                           |      |         |       |
|--------|--------|--------|---------|-------------------------------------------------------------------------------------------|------|---------|-------|
| M62782 | M62782 | 146734 | GEN-3CU | factor binding protein 4 (IGFBP4) mRNA, complete cds                                      | 908  | 852C>T  | 3     |
| M62982 | M62982 | 152391 | GEN-12  | Homo sapiens insulin-like growth factor binding protein 5 (IGFBP-5) mRNA, complete cds    | 1018 | 965G>A  | S322N |
| M62982 | M62982 | 152391 | GEN-12  | Lipoxygenases: 12-lipoxygenase (platelet)                                                 | 1145 | 1092T>G | S     |
| AKT1   | M63167 | 164730 | GEN-3D7 | Lipoxygenases: 12-lipoxygenase (platelet)                                                 | 934  | 736T>G  | S246A |
| AKT1   | M63167 | 164730 | GEN-3D7 | Human rac protein kinase alpha mRNA, complete cds                                         | 1964 | 1766G>A | 3     |
| M63509 | M63509 | 138380 | GEN-9G  | Human rac protein kinase alpha mRNA, complete cds                                         | 644  | 628A>T  | T210S |
| FGFR3  | M64347 | 134934 | GEN-3EX | Glutathione S-transferase M2 (muscle)                                                     | 3108 | 3108C>A | 3     |
| FGFR3  | M64347 | 134934 | GEN-3EX | Human novel growth factor receptor mRNA, 3 cds                                            | 3715 | 3715G>A | 3     |
| M68892 | M68892 | 147559 | GEN-15  | Human novel growth factor receptor mRNA, 3 cds                                            | 1327 | 1176C>T | S     |
| IGFBP6 | M69054 | 146735 | GEN-3J0 | Leukocyte integrin beta-7                                                                 | 751  | 751A>C  | 3     |
| IGFBP6 | M69054 | 146735 | GEN-3J0 | Human insulin-like growth factor binding protein 6 (IGFBP6) mRNA, complete mature peptide | 835  | 835A>C  | 3     |
| IGFBP6 | M69054 | 146735 | GEN-3J0 | Human insulin-like growth factor binding protein 6 (IGFBP6) mRNA, complete mature peptide | 850  | 850G>A  | 3     |
| M73554 | M73554 | 168461 | GEN-FY  | Human insulin-like growth factor binding protein 6 (IGFBP6) mRNA, complete mature peptide | 864  | 723G>A  | S     |
| M73554 | M73554 | 168461 | GEN-FY  | Cyclin D1                                                                                 | 1094 | 953A>C  | 3     |
| M73554 | M73554 | 168461 | GEN-FY  | Cyclin D1                                                                                 | 1094 | 953A>C  | 3     |
| M73554 | M73554 | 168461 | GEN-FY  | Cyclin D1                                                                                 | 1367 | 1226T>G | 3     |
| M73554 | M73554 | 168461 | GEN-FY  | Cyclin D1                                                                                 | 3899 | 3758T>G | 3     |
| M73554 | M73554 | 168461 | GEN-FY  | Cyclin D1                                                                                 | 4013 | 3872A>G | 3     |

|        |        |        |             |                                                                      |      |                     |        |
|--------|--------|--------|-------------|----------------------------------------------------------------------|------|---------------------|--------|
| SRD5A2 | M74047 | 264600 | GEN-<br>CDC | Human steroid 5-alpha-<br>reductase 2 (SRD5A2)<br>mRNA, complete cds | 2379 | 2352A>G             | 3      |
| M74091 | M74091 | 123838 | GEN-FZ      | G1/S-SPECIFIC CYCLIN C                                               | 41   | 42C>G               | 3      |
| CCNE   | M74093 | 123837 | GEN-<br>3MX | Human cyclin mRNA                                                    | 1195 | 1196C>T             | 3      |
| CCNE   | M74093 | 123837 | GEN-<br>3MX | Human cyclin mRNA                                                    | 1641 | 1642C>A             | 3      |
| M74782 | M74782 | 308385 | GEN-64      | Interleukin 3 receptor, alpha<br>(low affinity)                      | 1396 | 1250C>T             | 3      |
| MPG    | M74905 | 156565 | GEN-<br>3NL | Human 3-alkyladenine<br>DNA glycosylase (HAAG)                       | 254  | 108C>T              | S      |
| MPG    | M74905 | 156565 | GEN-<br>3NL | Human 3-alkyladenine<br>DNA glycosylase (HAAG)                       | 350  | 204G>A              | S      |
| MPG    | M74905 | 156565 | GEN-<br>3NL | Human 3-alkyladenine<br>DNA glycosylase (HAAG)                       | 413  | 267G>A              | S      |
| MPG    | M74905 | 156565 | GEN-<br>3NL | Human 3-alkyladenine<br>DNA glycosylase (HAAG)                       | 416  | 270C>T              | S      |
| MPG    | M74905 | 156565 | GEN-<br>3NL | Human 3-alkyladenine<br>DNA glycosylase (HAAG)                       | 546  | 400C>G              | P134A  |
| MPG    | M74905 | 156565 | GEN-<br>3NL | Human 3-alkyladenine<br>DNA glycosylase (HAAG)                       | 743  | 597C>T              | S      |
| M80646 | M80646 | 274180 | GEN-40      | Thromboxane synthase                                                 | 756  | 585G>C              | S      |
| M80646 | M80646 | 274180 | GEN-40      | Thromboxane synthase                                                 | 1240 | 1069C>G             | L357V  |
| M81695 | M81695 | 151510 | GEN-17      | Leukocyte integrin alpha-x                                           | 1834 | 1770G>C             | S      |
| M81695 | M81695 | 151510 | GEN-17      | Leukocyte integrin alpha-x                                           | 3282 | 3218C>T             | T1073M |
| M81695 | M81695 | 151510 | GEN-17      | Leukocyte integrin alpha-x                                           | 4213 | 4149C>G             | 3      |
| M84747 | M84747 | 300007 | GEN-45      | Interleukin 9 receptor                                               | 1273 | 1094G>A             | R365H  |
| TGFBR2 | M85079 | 190182 | GEN-<br>3ZS | Human TGF-beta type II<br>receptor mRNA, complete<br>cds             | 2045 | 1710A>C             | 3      |
| M90100 | M90100 | 600262 | GEN-1A      | Cyclooxygenase 2 COX2                                                | 2159 | 2062G>C             | 3      |
| M90100 | M90100 | 600262 | GEN-1A      | Cyclooxygenase 2 COX2                                                | 2186 | 2089-<br>2094ATATTA | 3      |



|        |        |        |         |                                                                       |      |                        |       |
|--------|--------|--------|---------|-----------------------------------------------------------------------|------|------------------------|-------|
| M90100 | M90100 | 600262 | GEN-1A  | Cyclooxygenase 2 COX2                                                 | 2186 | >ATATTA<br>2094delATAT | 3     |
| M90100 | M90100 | 600262 | GEN-1A  | Cyclooxygenase 2 COX2                                                 | 2230 | TA<br>2133A>G          | 3     |
| M90100 | M90100 | 600262 | GEN-1A  | Cyclooxygenase 2 COX2                                                 | 2339 | 2242T>C                | 3     |
| M90100 | M90100 | 600262 | GEN-1A  | Cyclooxygenase 2 COX2                                                 | 2409 | 2312G>A                | 3     |
| M90100 | M90100 | 600262 | GEN-1A  | Cyclooxygenase 2 COX2                                                 | 2726 | 2629C>T                | 3     |
| M90100 | M90100 | 600262 | GEN-1A  | Cyclooxygenase 2 COX2                                                 | 2983 | 2886C>T                | 3     |
| M90814 | M90814 | 123834 | GEN-GK  | Cyclin D3                                                             | 1648 | 1548G>A                | 3     |
| IL8RB  | M94582 | 146928 | GEN-49G | Interleukin 8 receptor                                                | 838  | 786T>C                 | S     |
| IL8RB  | M94582 | 146928 | GEN-49G | Interleukin 8 receptor                                                | 1262 | 1210C>T                | 3     |
| IL8RB  | M94582 | 146928 | GEN-49G | Interleukin 8 receptor                                                | 1494 | 1442A>G                | 3     |
| BRAF   | M95712 | 164757 | GEN-4AD | Human B-raf mRNA,<br>complete cds                                     | 284  | 223T>G                 | S75A  |
| M96234 | M96234 | 138333 | GEN-9J  | Glutathione S-transferase<br>M4                                       | 797  | 534T>C                 | S     |
| M96652 | M96652 | 147851 | GEN-65  | Interleukin 5 receptor alpha                                          | 883  | 634T>G                 | S212A |
| M98045 | M98045 | 136510 | GEN-4C3 | Homo sapiens<br>folypolyglutamate<br>synthetase mRNA,<br>complete cds | 802  | 732C>T                 | S     |
| M98045 | M98045 | 136510 | GEN-4C3 | Homo sapiens<br>folypolyglutamate<br>synthetase mRNA,<br>complete cds | 1747 | 1677G>T                | 3     |
| M98045 | M98045 | 136510 | GEN-4C3 | Homo sapiens<br>folypolyglutamate<br>synthetase mRNA,<br>complete cds | 1900 | 1830T>C                | 3     |
| M98045 | M98045 | 136510 | GEN-4C3 | Homo sapiens<br>folypolyglutamate<br>synthetase mRNA,<br>complete cds | 1900 | 1830T>C                | 3     |
| M98045 | M98045 | 136510 | GEN-4C3 | Homo sapiens<br>folypolyglutamate<br>synthetase mRNA,<br>complete cds | 1912 | 1842G>A                | 3     |

|        |        |        |         |                                                                                                                                   |      |         |     |
|--------|--------|--------|---------|-----------------------------------------------------------------------------------------------------------------------------------|------|---------|-----|
| M98045 | M98045 | 136510 | GEN-4C3 | complete cds<br>Homo sapiens<br>folypolyglutamate<br>synthetase mRNA,                                                             | 1995 | 1925C>G | 3   |
| M98539 | M98539 | 176803 | GEN-SW  | complete cds<br>prostaglandin D2 synthase<br>gene                                                                                 | 157  | 158C>A  | 3   |
| S72487 | S72487 | 131222 | GEN-3LD | orf1 5 to PD-<br>ECGF/TP...orf2 5 to PD-<br>ECGF/TP [human,<br>epidermoid carcinoma cell<br>line A431, mRNA, 3 genes,<br>1718 nt] | 183  | 19G>A   | D7N |
| S72487 | S72487 | 131222 | GEN-3LD | orf1 5 to PD-<br>ECGF/TP...orf2 5 to PD-<br>ECGF/TP [human,<br>epidermoid carcinoma cell<br>line A431, mRNA, 3 genes,<br>1718 nt] | 483  | 319C>T  | 3   |
| S72487 | S72487 | 131222 | GEN-3LD | orf1 5 to PD-<br>ECGF/TP...orf2 5 to PD-<br>ECGF/TP [human,<br>epidermoid carcinoma cell<br>line A431, mRNA, 3 genes,<br>1718 nt] | 601  | 437G>C  | 3   |
| S72487 | S72487 | 131222 | GEN-3LD | orf1 5 to PD-<br>ECGF/TP...orf2 5 to PD-<br>ECGF/TP [human,<br>epidermoid carcinoma cell<br>line A431, mRNA, 3 genes,<br>1718 nt] | 1299 | 1135G>A | 3   |
| PDCD2  | S78085 | 600866 | GEN-3QQ | PDCD2=programmed cell<br>death-2/Rp8 homolog<br>[human, fetal lung, mRNA,<br>1718 nt]                                             | 1180 | 1151G>A | 3   |
| U00672 | U00672 | 146933 | GEN-4A  | Interleukin 10 receptor                                                                                                           | 3377 | 3316A>C | 3   |
| U00672 | U00672 | 146933 | GEN-4A  | Interleukin 10 receptor                                                                                                           | 3524 | 3463A>G | 3   |
| U03858 | U03858 | 600007 | GEN-MDM | Fms-related tyrosine<br>kinase 3 ligand                                                                                           | 683  | 600C>T  | S   |
| U03858 | U03858 | 600007 | GEN-MDM | Fms-related tyrosine<br>kinase 3 ligand                                                                                           | 1016 | 933T>C  | 3   |

|       |        |        |         |                                                                |      |         |       |
|-------|--------|--------|---------|----------------------------------------------------------------|------|---------|-------|
| PI5   | U04313 | 154790 | GEN-14A | Human maspin mRNA, complete cds                                | 2496 | 2421G>C | 3     |
| NTRK3 | U05012 | 191316 | GEN-16V | Human receptor tyrosine kinase TrkC (NTRK3) mRNA, complete cds | 364  | 209G>A  | S70N  |
| NTRK3 | U05012 | 191316 | GEN-16V | Human receptor tyrosine kinase TrkC (NTRK3) mRNA, complete cds | 728  | 573C>T  | S     |
| NTRK3 | U05012 | 191316 | GEN-16V | Human receptor tyrosine kinase TrkC (NTRK3) mRNA, complete cds | 1613 | 1458C>T | S     |
| NTRK3 | U05012 | 191316 | GEN-16V | Human receptor tyrosine kinase TrkC (NTRK3) mRNA, complete cds | 1643 | 1488G>C | S     |
| DDH1  | U05598 | 600450 | GEN-184 | Human dihydrodiol dehydrogenase mRNA, complete cds             | 38   | 15C>T   | S     |
| DDH1  | U05598 | 600450 | GEN-184 | Human dihydrodiol dehydrogenase mRNA, complete cds             | 282  | 259A>T  | S87C  |
| DDH1  | U05598 | 600450 | GEN-184 | Human dihydrodiol dehydrogenase mRNA, complete cds             | 350  | 327C>T  | S     |
| DDH1  | U05598 | 600450 | GEN-184 | Human dihydrodiol dehydrogenase mRNA, complete cds             | 365  | 342T>C  | S     |
| DDH1  | U05598 | 600450 | GEN-184 | Human dihydrodiol dehydrogenase mRNA, complete cds             | 464  | 441G>A  | S     |
| DDH1  | U05598 | 600450 | GEN-184 | Human dihydrodiol dehydrogenase mRNA, complete cds             | 474  | 451A>G  | M151V |
| DDH1  | U05598 | 600450 | GEN-184 | Human dihydrodiol dehydrogenase mRNA, complete cds             | 532  | 509A>G  | H170R |
| DDH1  | U05598 | 600450 | GEN-184 | Human dihydrodiol dehydrogenase mRNA, complete cds             | 538  | 515T>A  | L172Q |
| DDH1  | U05598 | 600450 | GEN-184 | Human dihydrodiol dehydrogenase mRNA, complete cds             | 689  | 666T>C  | S     |

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|        |        |        |         |                                                                                         |      |         |       |
|--------|--------|--------|---------|-----------------------------------------------------------------------------------------|------|---------|-------|
| DDH1   | U05598 | 600450 | GEN-184 | Human dihydrodiol dehydrogenase mRNA, complete cds                                      | 806  | 783G>A  | S     |
| DDH1   | U05598 | 600450 | GEN-184 | Human dihydrodiol dehydrogenase mRNA, complete cds                                      | 872  | 849G>T  | S     |
| DDH1   | U05598 | 600450 | GEN-184 | Human dihydrodiol dehydrogenase mRNA, complete cds                                      | 952  | 929T>G  | I310S |
| DDH1   | U05598 | 600450 | GEN-184 | Human dihydrodiol dehydrogenase mRNA, complete cds                                      | 1020 | 997G>A  | 3     |
| DDH1   | U05598 | 600450 | GEN-184 | Human dihydrodiol dehydrogenase mRNA, complete cds                                      | 1035 | 1012G>A | 3     |
| DDH1   | U05598 | 600450 | GEN-184 | Human dihydrodiol dehydrogenase mRNA, complete cds                                      | 1112 | 1089C>T | 3     |
| U05875 | U05875 | 147569 | GEN-18J | Human clone pSK1 interferon gamma receptor accessory factor-1 (AF-1) mRNA, complete cds | 2047 | 1399C>G | 3     |
| U05875 | U05875 | 147569 | GEN-18J | Human clone pSK1 interferon gamma receptor accessory factor-1 (AF-1) mRNA, complete cds | 2087 | 1439T>C | 3     |
| XDH    | U06117 | 278300 | GEN-194 | Human xanthine dehydrogenase (XDH) mRNA, complete cds                                   | 3951 | 3888C>G | S     |
| U09178 | U09178 | 274270 | GEN-HA  | Dihydropyrimidine Dehydrogenase                                                         | 166  | 85T>C   | C29R  |
| U09178 | U09178 | 274270 | GEN-HA  | Dihydropyrimidine Dehydrogenase                                                         | 166  | 85T>C   | C29R  |
| U09178 | U09178 | 274270 | GEN-HA  | Dihydropyrimidine Dehydrogenase                                                         | 577  | 496A>G  | M166V |
| U09178 | U09178 | 274270 | GEN-HA  | Dihydropyrimidine Dehydrogenase                                                         | 638  | 557A>G  | Y186C |
| U09178 | U09178 | 274270 | GEN-HA  | Dihydropyrimidine Dehydrogenase                                                         | 1708 | 1627A>G | I543V |
| U09178 | U09178 | 274270 | GEN-HA  | Dihydropyrimidine Dehydrogenase                                                         | 3432 | 3351T>C | 3     |

|        |        |        |             |                                                                               |      |         |       |
|--------|--------|--------|-------------|-------------------------------------------------------------------------------|------|---------|-------|
| U09178 | U09178 | 274270 | GEN-HA      | Dihydropyrimidine<br>Dehydrogenase                                            | 3730 | 3649G>A | 3     |
| U09178 | U09178 | 274270 | GEN-HA      | Dihydropyrimidine<br>Dehydrogenase                                            | 3925 | 3844A>G | 3     |
| U09178 | U09178 | 274270 | GEN-HA      | Dihydropyrimidine<br>Dehydrogenase                                            | 3937 | 3856T>C | 3     |
| U09579 | U09579 | 116899 | GEN-<br>1GZ | Human melanoma<br>differentiation associated<br>(mda-6) mRNA, complete<br>cds | 609  | 515C>T  | 3     |
| U09579 | U09579 | 116899 | GEN-<br>1GZ | Human melanoma<br>differentiation associated<br>(mda-6) mRNA, complete<br>cds | 1875 | 1781G>A | 3     |
| U09579 | U09579 | 116899 | GEN-<br>1GZ | Human melanoma<br>differentiation associated<br>(mda-6) mRNA, complete<br>cds | 1877 | 1783C>G | 3     |
| U09759 | U09759 | 602896 | GEN-<br>1HA | Human protein kinase<br>(JNK2) mRNA, complete<br>cds                          | 303  | 152A>G  | N51S  |
| U09759 | U09759 | 602896 | GEN-<br>1HA | Human protein kinase<br>(JNK2) mRNA, complete<br>cds                          | 1079 | 928A>G  | I310V |
| U09759 | U09759 | 602896 | GEN-<br>1HA | Human protein kinase<br>(JNK2) mRNA, complete<br>cds                          | 1280 | 1129C>T | P377S |
| U09759 | U09759 | 602896 | GEN-<br>1HA | Human protein kinase<br>(JNK2) mRNA, complete<br>cds                          | 1559 | 1408C>T | 3     |
| U09806 | U09806 | None   | GEN-<br>4FZ | Human<br>methylenetetrahydrofolate<br>reductase mRNA, partial<br>cds          | 120  | 120T>C  | S     |
| U09806 | U09806 | None   | GEN-<br>4FZ | Human<br>methylenetetrahydrofolate<br>reductase mRNA, partial<br>cds          | 473  | 473G>A  | R158Q |
| U09806 | U09806 | None   | GEN-<br>4FZ | Human<br>methylenetetrahydrofolate<br>reductase mRNA, partial<br>cds          | 550  | 550C>T  | F     |

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| U09806 | U09806 | None   | GEN-4FZ | cds<br>Human<br>methylenetetrahydrofolate<br>reductase mRNA, partial                        | 668  | 668C>T  | A223V |
| U09806 | U09806 | None   | GEN-4FZ | cds<br>Human<br>methylenetetrahydrofolate<br>reductase mRNA, partial                        | 1059 | 1059T>C | S     |
| U09806 | U09806 | None   | GEN-4FZ | cds<br>Human<br>methylenetetrahydrofolate<br>reductase mRNA, partial                        | 1289 | 1289C>A | E430A |
| U09806 | U09806 | None   | GEN-4FZ | cds<br>Human<br>methylenetetrahydrofolate<br>reductase mRNA, partial                        | 1308 | 1308T>C | 3     |
| U09850 | U09850 | 603433 | GEN-1HD | cds<br>Human zinc finger protein<br>(ZNF143) mRNA, complete                                 | 1383 | 1346G>A | G449D |
| U09850 | U09850 | 603433 | GEN-1HD | cds<br>Human zinc finger protein<br>(ZNF143) mRNA, complete                                 | 2443 | 2406C>T | 3     |
| U09850 | U09850 | 603433 | GEN-1HD | cds<br>Human zinc finger protein<br>(ZNF143) mRNA, complete                                 | 2950 | 2913A>G | 3     |
| U09850 | U09850 | 603433 | GEN-1HD | cds<br>Human zinc finger protein<br>(ZNF143) mRNA, complete                                 | 3001 | 2964G>A | 3     |
| U09850 | U09850 | 603433 | GEN-1HD | cds<br>Human zinc finger protein<br>(ZNF143) mRNA, complete                                 | 3120 | 3083T>C | 3     |
| U09850 | U09850 | 603433 | GEN-1HD | cds<br>Human zinc finger protein<br>(ZNF143) mRNA, complete                                 | 3745 | 3708T>C | 3     |
| THPO   | U11025 | 600044 | GEN-1JW | cds<br>Human megakaryocyte<br>growth and development<br>factor (MGDF) mRNA,<br>complete cds | 76   | 41T>C   | L14P  |
| THPO   | U11025 | 600044 | GEN-1JW | cds<br>Human megakaryocyte<br>growth and development<br>factor (MGDF) mRNA,<br>complete cds | 172  | 137G>A  | R46K  |

|        |        |        |         |                                                                                                                 |      |         |       |
|--------|--------|--------|---------|-----------------------------------------------------------------------------------------------------------------|------|---------|-------|
| THPO   | U11025 | 600044 | GEN-1JW | factor (MGDF) mRNA, complete cds<br>Human megakaryocyte growth and development factor (MGDF) mRNA, complete cds | 382  | 347G>A  | G116E |
| THPO   | U11025 | 600044 | GEN-1JW | Human megakaryocyte growth and development factor (MGDF) mRNA, complete cds                                     | 674  | 639T>A  | S     |
| THPO   | U11025 | 600044 | GEN-1JW | Human megakaryocyte growth and development factor (MGDF) mRNA, complete cds                                     | 1132 | 1097G>A | 3     |
| U11791 | U11791 | 601953 | GEN-HF  | Cyclin H                                                                                                        | 823  | 763A>G  | M255V |
| TPMT   | U12387 | 187680 | GEN-1LY | Human thiopurine methyltransferase (TPMT) mRNA, complete cds                                                    | 536  | 460G>A  | A154T |
| TPMT   | U12387 | 187680 | GEN-1LY | Human thiopurine methyltransferase (TPMT) mRNA, complete cds                                                    | 795  | 719A>G  | Y240C |
| TPMT   | U12387 | 187680 | GEN-1LY | Human thiopurine methyltransferase (TPMT) mRNA, complete cds                                                    | 1085 | 1009T>C | 3     |
| TPMT   | U12387 | 187680 | GEN-1LY | Human thiopurine methyltransferase (TPMT) mRNA, complete cds                                                    | 1336 | 1260C>T | 3     |
| TPMT   | U12387 | 187680 | GEN-1LY | Human thiopurine methyltransferase (TPMT) mRNA, complete cds                                                    | 1373 | 1297G>A | 3     |
| U13737 | U13737 | 600636 | GEN-1PC | Human cysteine protease CPP32 isoform alpha mRNA, complete cds                                                  | 2356 | 2132A>C | 3     |
| U13737 | U13737 | 600636 | GEN-1PC | Human cysteine protease CPP32 isoform alpha mRNA, complete cds                                                  | 2535 | 2311C>T | 3     |
| BRCA1  | U14680 | 113705 | GEN-1S1 | Human breast and ovarian cancer susceptibility (BRCA1) mRNA, complete cds                                       | 4427 | 4308T>C | S     |
| U19251 | U19251 | 600355 | GEN-221 | Homo sapiens neuronal                                                                                           | 2223 | 1932T>G | F644L |

|        |        |        |         |                                                                       |      |                |       |
|--------|--------|--------|---------|-----------------------------------------------------------------------|------|----------------|-------|
| U19251 | U19251 | 600355 | GEN-221 | apoptosis inhibitory protein mRNA, complete cds                       | 3046 | 2755C>T        | P919S |
| U19251 | U19251 | 600355 | GEN-221 | Homo sapiens neuronal apoptosis inhibitory protein mRNA, complete cds | 5503 | 5212A>G        | 3     |
| U19251 | U19251 | 600355 | GEN-221 | apoptosis inhibitory protein mRNA, complete cds                       | 5634 | 5343A>G        | 3     |
| U19251 | U19251 | 600355 | GEN-221 | Homo sapiens neuronal apoptosis inhibitory protein mRNA, complete cds | 5644 | 5353A>G        | 3     |
| U19487 | U19487 | 176804 | GEN-41  | Homo sapiens neuronal apoptosis inhibitory protein mRNA, complete cds | 231  | 75A>T          | S     |
| U19720 | U19720 | 600424 | GEN-I1  | PROSTAGLANDIN E2 RECEPTOR, EP2 SUBTYPE                                | 53   | (-43)T>C       | 5     |
| U19720 | U19720 | 600424 | GEN-I1  | Folate Transporter (SLC19A1)                                          | 175  | 80G>A          | R27H  |
| U19720 | U19720 | 600424 | GEN-I1  | Folate Transporter (SLC19A1)                                          | 175  | 80G>A          | R27H  |
| U19720 | U19720 | 600424 | GEN-I1  | Folate Transporter (SLC19A1)                                          | 341  | 246C>G         | S     |
| U19720 | U19720 | 600424 | GEN-I1  | Folate Transporter (SLC19A1)                                          | 791  | 696C>T         | S     |
| U19720 | U19720 | 600424 | GEN-I1  | Folate Transporter (SLC19A1)                                          | 1067 | 972G>A         | S     |
| U19720 | U19720 | 600424 | GEN-I1  | Folate Transporter (SLC19A1)                                          | 2100 | 2005^2006ins G | F     |
| U19720 | U19720 | 600424 | GEN-I1  | Folate Transporter (SLC19A1)                                          | 2582 | 2487T>G        | 3     |
| U19720 | U19720 | 600424 | GEN-I1  | Folate Transporter (SLC19A1)                                          | 2582 | 2487T>G        | 3     |
| U19720 | U19720 | 600424 | GEN-I1  | Folate Transporter (SLC19A1)                                          | 2617 | 2522C>T        | 3     |
| U19720 | U19720 | 600424 | GEN-I1  | Folate Transporter (SLC19A1)                                          | 2617 | 2522C>T        | 3     |
| U19720 | U19720 | 600424 | GEN-I1  | Folate Transporter (SLC19A1)                                          | 2652 | 2557T>C        | 3     |



|        |        |        |         |                                                                         |      |         |       |
|--------|--------|--------|---------|-------------------------------------------------------------------------|------|---------|-------|
| U19775 | U19775 | 600289 | GEN-22C | Human MAP kinase Mxi2 (MXI2) mRNA, complete cds                         | 731  | 688G>A  | D230N |
| U20536 | U20536 | 601532 | GEN-23K | Human cysteine protease Mch2 isoform alpha (Mch2) mRNA, complete cds    | 982  | 904C>T  | 3     |
| U20536 | U20536 | 601532 | GEN-23K | Human cysteine protease Mch2 isoform alpha (Mch2) mRNA, complete cds    | 1117 | 1039G>A | 3     |
| U20536 | U20536 | 601532 | GEN-23K | Human cysteine protease Mch2 isoform alpha (Mch2) mRNA, complete cds    | 1322 | 1244T>C | 3     |
| U20536 | U20536 | 601532 | GEN-23K | Human cysteine protease Mch2 isoform alpha (Mch2) mRNA, complete cds    | 1363 | 1285T>C | 3     |
| U24231 | U24231 | None   | GEN-289 | Human Fas-associated death domain-containing protein mRNA, complete cds | 1312 | 1183G>A | 3     |
| U25029 | U25029 | 138040 | GEN-82  | Glucocorticoid receptor alpha                                           | 335  | 335C>T  | 3     |
| U25029 | U25029 | 138040 | GEN-82  | Glucocorticoid receptor alpha                                           | 386  | 386T>C  | 3     |
| U25029 | U25029 | 138040 | GEN-82  | Glucocorticoid receptor alpha                                           | 1069 | 1069C>T | 3     |
| CDKN2A | U26727 | 600160 | GEN-2BC | Human p16INK4/MTS1 mRNA, complete cds                                   | 311  | 284C>A  | T95N  |
| CDKN2A | U26727 | 600160 | GEN-2BC | Human p16INK4/MTS1 mRNA, complete cds                                   | 570  | 543G>C  | 3     |
| CDKN2A | U26727 | 600160 | GEN-2BC | Human p16INK4/MTS1 mRNA, complete cds                                   | 643  | 616C>T  | 3     |
| U27467 | U27467 | 601056 | GEN-2BX | Human Bcl-2 related (Bfl-1) mRNA, complete cds                          | 476  | 442T>C  | F148L |
| U27467 | U27467 | 601056 | GEN-2BX | Human Bcl-2 related (Bfl-1) mRNA, complete cds                          | 481  | 447A>G  | S     |
| U27467 | U27467 | 601056 | GEN-2BX | Human Bcl-2 related (Bfl-1) mRNA, complete cds                          | 542  | 508C>G  | L170V |
| U27467 | U27467 | 601056 | GEN-2BX | Human Bcl-2 related (Bfl-1) mRNA, complete cds                          | 578  | 544C>T  | 3     |
| U27467 | U27467 | 601056 | GEN-2BX | Human Bcl-2 related (Bfl-1) mRNA, complete cds                          | 614  | 580T>C  | 3     |

|        |        |        |         |                                                             |      |          |       |
|--------|--------|--------|---------|-------------------------------------------------------------|------|----------|-------|
| U27467 | U27467 | 601056 | GEN-2BX | Human Bcl-2 related (Bfl-1) mRNA, complete cds              | 616  | 582G>A   | 3     |
| CSNK1D | U29171 | 600864 | GEN-2E2 | Human casein kinase I delta mRNA, complete cds              | 1612 | 1435C>A  | 3     |
| U31628 | U31628 | 601070 | GEN-4J  | Interleukin 15 receptor alpha chain                         | 1250 | 1168G>T  | 3     |
| U32324 | U32324 | 600939 | GEN-4K  | interleukin 11 receptor alpha chain                         | 1266 | 1205C>A  | P402Q |
| U32324 | U32324 | 600939 | GEN-4K  | interleukin 11 receptor alpha chain                         | 1513 | 1452C>T  | 3     |
| U33286 | U33286 | 601342 | GEN-IM  | Chromosome segregation gene homolog CAS                     | 54   | (-70)A>G | 5     |
| U33286 | U33286 | 601342 | GEN-IM  | Chromosome segregation gene homolog CAS                     | 821  | 698G>A   | G233D |
| U33286 | U33286 | 601342 | GEN-IM  | Chromosome segregation gene homolog CAS                     | 3127 | 3004T>C  | 3     |
| FGF8   | U36223 | 600483 | GEN-2MX | Human fibroblast growth factor 8 (FGF-8) mRNA, complete cds | 300  | 291T>C   | S     |
| FGF8   | U36223 | 600483 | GEN-2MX | Human fibroblast growth factor 8 (FGF-8) mRNA, complete cds | 645  | 636G>C   | S     |
| FGF8   | U36223 | 600483 | GEN-2MX | Human fibroblast growth factor 8 (FGF-8) mRNA, complete cds | 648  | 639A>G   | S     |
| U37448 | U37448 | 601761 | GEN-2OC | Human Mch3 isoform alpha (Mch3) mRNA, complete cds          | 736  | 693G>A   | S     |
| U37448 | U37448 | 601761 | GEN-2OC | Human Mch3 isoform alpha (Mch3) mRNA, complete cds          | 1285 | 1242T>C  | 3     |
| U37448 | U37448 | 601761 | GEN-2OC | Human Mch3 isoform alpha (Mch3) mRNA, complete cds          | 1294 | 1251T>C  | 3     |
| U37448 | U37448 | 601761 | GEN-2OC | Human Mch3 isoform alpha (Mch3) mRNA, complete cds          | 1580 | 1537A>T  | 3     |
| U37448 | U37448 | 601761 | GEN-2OC | Human Mch3 isoform alpha (Mch3) mRNA, complete cds          | 1621 | 1578G>T  | 3     |
| U37448 | U37448 | 601761 | GEN-2OC | Human Mch3 isoform alpha (Mch3) mRNA, complete cds          | 1715 | 1672G>A  | 3     |

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|--------|--------|--------|-------------|-------------------------------------------------------------------------------|------|---------|-------|
| U37448 | U37448 | 601761 | 2OC         | alpha (Mch3) mRNA,<br>complete cds                                            | 1764 | 1721G>A | 3     |
| U37518 | U37518 | None   | GEN-<br>2OC | Human Mch3 isoform<br>alpha (Mch3) mRNA,<br>complete cds                      | 912  | 825C>T  | S     |
| U37518 | U37518 | None   | GEN-<br>2OG | Human TNF-related<br>apoptosis inducing ligand<br>TRAIL mRNA, complete<br>cds | 1140 | 1053A>G | 3     |
| U37518 | U37518 | None   | GEN-<br>2OG | Human TNF-related<br>apoptosis inducing ligand<br>TRAIL mRNA, complete<br>cds | 1289 | 1202C>A | 3     |
| U37518 | U37518 | None   | GEN-<br>2OG | Human TNF-related<br>apoptosis inducing ligand<br>TRAIL mRNA, complete<br>cds | 1525 | 1438G>A | 3     |
| U37518 | U37518 | None   | GEN-<br>2OG | Human TNF-related<br>apoptosis inducing ligand<br>TRAIL mRNA, complete<br>cds | 1588 | 1501G>A | 3     |
| U37518 | U37518 | None   | GEN-<br>2OG | Human TNF-related<br>apoptosis inducing ligand<br>TRAIL mRNA, complete<br>cds | 1595 | 1508C>T | 3     |
| U39656 | U39656 | 601254 | GEN-<br>2Q8 | Human MAP kinase<br>6 (MKK6) mRNA, complete<br>cds                            | 431  | 91A>C   | S     |
| U39656 | U39656 | 601254 | GEN-<br>2Q8 | Human MAP kinase<br>6 (MKK6) mRNA, complete<br>cds                            | 713  | 373G>A  | V125M |
| U43030 | U43030 | 600435 | GEN-LFI     | Human cardiotrophin-1<br>(CTF1) mRNA, complete<br>cds                         | 1404 | 1372C>T | 3     |
| U43142 | U43142 | 601528 | GEN-<br>2UM | Human vascular<br>endothelial growth factor<br>related protein VRP<br>cds     | 1499 | 1128C>T | S     |

|        |        |        |         |                                                                                 |      |         |       |
|--------|--------|--------|---------|---------------------------------------------------------------------------------|------|---------|-------|
| U45878 | U45878 | 601721 | GEN-2WJ | mRNA, complete cds<br>Human inhibitor of apoptosis protein 1 mRNA, complete cds | 2281 | 1833G>A | 3     |
| U45878 | U45878 | 601721 | GEN-2WJ | Human inhibitor of apoptosis protein 1 mRNA, complete cds                       | 2820 | 2372C>G | 3     |
| U45879 | U45879 | 601712 | GEN-2WI | Human inhibitor of apoptosis protein 2 mRNA, complete cds                       | 748  | 511T>G  | S171A |
| U45879 | U45879 | 601712 | GEN-2WI | Human inhibitor of apoptosis protein 2 mRNA, complete cds                       | 835  | 598T>G  | S200A |
| U47634 | U47634 | None   | GEN-2XR | Human beta-tubulin class III isotype (beta-3) mRNA, complete cds                | 1005 | 1005C>T | S     |
| U47634 | U47634 | None   | GEN-2XR | Human beta-tubulin class III isotype (beta-3) mRNA, complete cds                | 1035 | 1035C>T | S     |
| U47634 | U47634 | None   | GEN-2XR | Human beta-tubulin class III isotype (beta-3) mRNA, complete cds                | 1431 | 1431T>C | 3     |
| U47634 | U47634 | None   | GEN-2XR | Human beta-tubulin class III isotype (beta-3) mRNA, complete cds                | 1502 | 1502G>A | 3     |
| U54831 | U54831 | 126431 | GEN-8W  | Topoisomerase II beta                                                           | 127  | 127A>G  | T43A  |
| U54831 | U54831 | 126431 | GEN-8W  | Topoisomerase II beta                                                           | 1002 | 1002T>C | S     |
| U55206 | U55206 | None   | GEN-35Z | Homo sapiens human gamma-glutamyl hydrolase (hGH) mRNA, complete cds            | 75   | 16T>C   | C6R   |
| U55206 | U55206 | None   | GEN-35Z | Homo sapiens human gamma-glutamyl hydrolase (hGH) mRNA, complete cds            | 150  | 91G>A   | A31T  |
| U55206 | U55206 | None   | GEN-35Z | Homo sapiens human gamma-glutamyl hydrolase (hGH) mRNA, complete cds            | 511  | 452C>T  | T151I |
| U55206 | U55206 | None   | GEN-35Z | Homo sapiens human gamma-glutamyl hydrolase                                     | 1161 | 1102A>G | 3     |

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|--------|--------|--------|---------|-----------------------------------------------------------------------------------|------|---------|--------|
| U56390 | U56390 | 602234 | GEN-36X | (hGH) mRNA, complete cds<br>Human cysteine protease ICE-LAP6 mRNA, complete cds   | 411  | 408C>T  | S      |
| U60519 | U60519 | 601762 | GEN-3AZ | Human apoptotic cysteine protease Mch4 (Mch4) mRNA, complete cds                  | 304  | 157G>A  | E53K   |
| U60519 | U60519 | 601762 | GEN-3AZ | Human apoptotic cysteine protease Mch4 (Mch4) mRNA, complete cds                  | 324  | 177A>G  | S      |
| U70136 | U70136 | 600044 | GEN-4R  | Thrombopoietin                                                                    | 4138 | 4105G>T | A1369S |
| U70136 | U70136 | 600044 | GEN-4R  | Thrombopoietin                                                                    | 4141 | 4108T>A | F1370I |
| U70321 | U70321 | None   | GEN-3K9 | Human herpesvirus entry mediator mRNA, complete cds                               | 343  | 50G>A   | R17K   |
| U70321 | U70321 | None   | GEN-3K9 | Human herpesvirus entry mediator mRNA, complete cds                               | 1014 | 721G>A  | V241I  |
| U70321 | U70321 | None   | GEN-3K9 | Human herpesvirus entry mediator mRNA, complete cds                               | 1218 | 925A>G  | 3      |
| U70321 | U70321 | None   | GEN-3K9 | Human herpesvirus entry mediator mRNA, complete cds                               | 1249 | 956C>T  | 3      |
| U70321 | U70321 | None   | GEN-3K9 | Human herpesvirus entry mediator mRNA, complete cds                               | 1453 | 1160G>A | 3      |
| U77088 | U77088 | 188250 | GEN-K4  | Thymidine kinase 2                                                                | 1480 | 1472T>C | 3      |
| U79269 | U79269 | 123829 | GEN-K7  | Cyclin-Dependent Protein Kinase                                                   | 1281 | 972A>T  | 3      |
| U81375 | U81375 | 602193 | GEN-3VO | Human placental equilibrative nucleoside transporter 1 (hENT1) mRNA, complete cds | 1989 | 1811G>A | 3      |
| U81375 | U81375 | 602193 | GEN-3VO | Human placental equilibrative nucleoside transporter 1 (hENT1) mRNA, complete cds | 1996 | 1818C>T | 3      |
| U81375 | U81375 | 602193 | GEN-3VO | Human placental equilibrative nucleoside transporter 1 (hENT1) mRNA, complete cds | 2045 | 1867T>C | 3      |

|        |        |        |         |                                                                  |      |          |       |
|--------|--------|--------|---------|------------------------------------------------------------------|------|----------|-------|
| IFNB1  | V00546 | 147640 | GEN-TV  | transporter 1 (hENT1) mRNA, complete cds                         | 474  | 410T>G   | L137R |
| V00548 | V00548 | 147562 | GEN-P2  | Messenger RNA for human fibroblast interferon                    | 119  | 119G>A   | R40K  |
| V00594 | V00594 | 156360 | GEN-P6  | Human messenger RNA for leukocyte (alpha-2) interferon           | 320  | 263G>C   | 3     |
| EGFR   | X00663 | 131550 | GEN-U4  | Human mRNA for metallothionein from cadmium-treated cells        | 1136 | 1136G>A  | R379K |
| EGFR   | X00663 | 131550 | GEN-U4  | Human mRNA fragment for epidermal growth factor (EGF) receptor   | 1935 | 1935A>G  | S     |
| EGFR   | X00663 | 131550 | GEN-U4  | Human mRNA fragment for epidermal growth factor (EGF) receptor   | 2283 | 2283C>T  | S     |
| X00734 | X00734 | None   | GEN-MST | Human beta-tubulin gene (5-beta) with ten Alu family members     | 1059 | 1059G>T  | S     |
| X00737 | X00737 | 164050 | GEN-P8  | Human mRNA for purine nucleoside phosphorylase (PNP; EC 2.4.2.1) | 59   | (-51)T>G | 5     |
| X00737 | X00737 | 164050 | GEN-P8  | Human mRNA for purine nucleoside phosphorylase (PNP; EC 2.4.2.1) | 169  | 60T>C    | S     |
| X00737 | X00737 | 164050 | GEN-P8  | Human mRNA for purine nucleoside phosphorylase (PNP; EC 2.4.2.1) | 260  | 151A>G   | S51G  |
| X00737 | X00737 | 164050 | GEN-P8  | Human mRNA for purine nucleoside phosphorylase (PNP; EC 2.4.2.1) | 280  | 171T>C   | S     |
| X00737 | X00737 | 164050 | GEN-P8  | Human mRNA for purine nucleoside phosphorylase (PNP; EC 2.4.2.1) | 1254 | 1145G>A  | 3     |
| X01060 | X01060 | 190010 | GEN-6C  | Transferrin receptor (p90, CD71)                                 | 687  | 424A>G   | S142G |
| X01060 | X01060 | 190010 | GEN-6C  | Transferrin receptor (p90, CD71)                                 | 2823 | 2560delT | F     |

|        |        |        |        |                                                           |      |           |       |
|--------|--------|--------|--------|-----------------------------------------------------------|------|-----------|-------|
| X01060 | X01060 | 190010 | GEN-6C | Transferrin receptor (p90, CD71)                          | 3766 | 3503T>G   | 3     |
| X01060 | X01060 | 190010 | GEN-6C | Transferrin receptor (p90, CD71)                          | 4122 | 3859A>C   | 3     |
| X01060 | X01060 | 190010 | GEN-6C | Transferrin receptor (p90, CD71)                          | 4147 | 3884G>A   | 3     |
| X01060 | X01060 | 190010 | GEN-6C | Transferrin receptor (p90, CD71)                          | 4247 | 3984T>C   | 3     |
| X01060 | X01060 | 190010 | GEN-6C | Transferrin receptor (p90, CD71)                          | 4309 | 4046T>A   | 3     |
| X01060 | X01060 | 190010 | GEN-6C | Transferrin receptor (p90, CD71)                          | 4381 | 4118A>G   | 3     |
| X01060 | X01060 | 190010 | GEN-6C | Transferrin receptor (p90, CD71)                          | 4547 | 4284G>A   | 3     |
| X01060 | X01060 | 190010 | GEN-6C | Transferrin receptor (p90, CD71)                          | 4619 | 4356T>G   | 3     |
| X01060 | X01060 | 190010 | GEN-6C | Transferrin receptor (p90, CD71)                          | 4726 | 4463A>T   | 3     |
| X01060 | X01060 | 190010 | GEN-6C | Transferrin receptor (p90, CD71)                          | 4766 | 4503C>T   | 3     |
| X01394 | X01394 | 191160 | GEN-4Y | Tumor necrosis factor                                     | 125  | (-28)C>T  | 5     |
| X01586 | X01586 | 147680 | GEN-PC | Interleukin 2                                             | 332  | 225T>G    | H75Q  |
| X01586 | X01586 | 147680 | GEN-PC | Interleukin 2                                             | 563  | 456G>A    | S     |
| X02308 | X02308 | 188350 | GEN-KL | Thymidylate synthetase                                    | 1066 | 961T>C    | 3     |
| X02308 | X02308 | 188350 | GEN-KL | Thymidylate synthetase                                    | 1066 | 961T>C    | 3     |
| X02308 | X02308 | 188350 | GEN-KL | Thymidylate synthetase                                    | 1136 | 1031A>G   | 3     |
| X02308 | X02308 | 188350 | GEN-KL | Thymidylate synthetase                                    | 1136 | 1031A>G   | 3     |
| X02308 | X02308 | 188350 | GEN-KL | Thymidylate synthetase                                    | 1497 | 1392T>A   | 3     |
| X02469 | X02469 | 191170 | GEN-PF | Human mRNA for p53 cellular tumor antigen                 | 350  | 215C>G    | P72R  |
| X02469 | X02469 | 191170 | GEN-PF | Human mRNA for p53 cellular tumor antigen                 | 953  | 818G>A    | R273H |
| NRAS   | X02751 | 164790 | GEN-XG | Human N-ras mRNA and flanking regions                     | 221  | (-506)A>G | 5     |
| NRAS   | X02751 | 164790 | GEN-XG | Human N-ras mRNA and flanking regions                     | 390  | (-337)C>A | 5     |
| X02812 | X02812 | 190180 | GEN-XR | Human mRNA for transforming growth factor-beta (TGF-beta) | 870  | 29C>T     | P10L  |
| X02812 | X02812 | 190180 | GEN-XR | Human mRNA for transforming growth factor-beta (TGF-beta) | 979  | 138C>G    | I46M  |

|        |        |        |        |                                                                                                         |      |                 |       |
|--------|--------|--------|--------|---------------------------------------------------------------------------------------------------------|------|-----------------|-------|
| X02812 | X02812 | 190180 | GEN-XR | transforming growth factor-beta (TGF-beta)<br>Human mRNA for transforming growth factor-beta (TGF-beta) | 1632 | 791C>T          | T264I |
| X02812 | X02812 | 190180 | GEN-XR | transforming growth factor-beta (TGF-beta)<br>Human mRNA for transforming growth factor-beta (TGF-beta) | 1807 | 966C>T          | S     |
| X02812 | X02812 | 190180 | GEN-XR | transforming growth factor-beta (TGF-beta)<br>Human mRNA for transforming growth factor-beta (TGF-beta) | 1930 | 1089G>A         | S     |
| X02812 | X02812 | 190180 | GEN-XR | transforming growth factor-beta (TGF-beta)<br>Human mRNA for transforming growth factor-beta (TGF-beta) | 1942 | 1101C>T         | S     |
| X02812 | X02812 | 190180 | GEN-XR | transforming growth factor-beta (TGF-beta)<br>Human mRNA for transforming growth factor-beta (TGF-beta) | 2013 | 1172G>A         | S391N |
| X03635 | X03635 | 133430 | GEN-50 | estrogen receptors                                                                                      | 390  | 30T>C           | S     |
| X03635 | X03635 | 133430 | GEN-50 | estrogen receptors                                                                                      | 390  | 30T>C           | S     |
| X03635 | X03635 | 133430 | GEN-50 | estrogen receptors                                                                                      | 424  | 64G>C           | E22Q  |
| X03635 | X03635 | 133430 | GEN-50 | estrogen receptors                                                                                      | 617  | 257C>T          | A86V  |
| X03635 | X03635 | 133430 | GEN-50 | estrogen receptors                                                                                      | 621  | 261G>C          | S     |
| X03635 | X03635 | 133430 | GEN-50 | estrogen receptors                                                                                      | 829  | 469C>T          | F     |
| X03635 | X03635 | 133430 | GEN-50 | estrogen receptors                                                                                      | 1335 | 975C>G          | S     |
| X03635 | X03635 | 133430 | GEN-50 | estrogen receptors                                                                                      | 1335 | 975C>G          | S     |
| X03635 | X03635 | 133430 | GEN-50 | estrogen receptors                                                                                      | 1451 | 1091T>A         | V364E |
| X03635 | X03635 | 133430 | GEN-50 | estrogen receptors                                                                                      | 1674 | 1314G>A         | M438I |
| X03635 | X03635 | 133430 | GEN-50 | estrogen receptors                                                                                      | 2142 | 1782A>G         | S     |
| X03635 | X03635 | 133430 | GEN-50 | estrogen receptors                                                                                      | 2354 | 1994A>G         | 3     |
| X03635 | X03635 | 133430 | GEN-50 | estrogen receptors                                                                                      | 2550 | 2190A>C         | 3     |
| X03635 | X03635 | 133430 | GEN-50 | estrogen receptors                                                                                      | 2733 | 2373C>G         | 3     |
| X03635 | X03635 | 133430 | GEN-50 | estrogen receptors                                                                                      | 3181 | 2821T>C         | 3     |
| X03635 | X03635 | 133430 | GEN-50 | estrogen receptors                                                                                      | 3338 | 2978C>T         | 3     |
| X03635 | X03635 | 133430 | GEN-50 | estrogen receptors                                                                                      | 3652 | 3292-3294CCT>CC | 3     |
| X03635 | X03635 | 133430 | GEN-50 | estrogen receptors                                                                                      | 3652 | 3292-T          | 3     |
| X03635 | X03635 | 133430 | GEN-50 | estrogen receptors                                                                                      | 3896 | 3294delCCT      | 3     |
|        |        |        |        | estrogen receptors                                                                                      |      | 3536C>A         |       |



|        |        |        |         |                                                                          |      |          |       |
|--------|--------|--------|---------|--------------------------------------------------------------------------|------|----------|-------|
| X03635 | X03635 | 133430 | GEN-50  | estrogen receptors                                                       | 4378 | 4018T>C  | 3     |
| X03635 | X03635 | 133430 | GEN-50  | estrogen receptors                                                       | 6287 | 5927T>C  | 3     |
| X03663 | X03663 | 164770 | GEN-51  | Colony stimulating factor 1 receptor                                     | 3732 | 3432T>C  | 3     |
| X03663 | X03663 | 164770 | GEN-51  | Colony stimulating factor 1 receptor                                     | 3951 | 3651C>A  | 3     |
| X04571 | X04571 | 131530 | GEN-KY0 | Human mRNA for kidney epidermal growth factor (EGF) precursor            | 4507 | 4071G>A  | 3     |
| X04707 | X04707 | 190160 | GEN-CCA | Human c-erb-A mRNA for thyroid hormone receptor                          | 1295 | 995T>C   | I332T |
| ARAF1  | X04790 | 311010 | GEN-15C | Human mRNA for A-raf-1 oncogene                                          | 1659 | 1465C>T  | F     |
| KIT    | X06182 | 164920 | GEN-19B | Human c-kit proto-oncogene mRNA                                          | 4656 | 4635G>T  | 3     |
| ITGA5  | X06256 | 135620 | GEN-19B | Human mRNA for fibronectin receptor alpha subunit                        | 2562 | 2539C>A  | L847I |
| X06318 | X06318 | 176970 | GEN-KY  | Protein kinase C, beta 1                                                 | 83   | (-54)G>C | 5     |
| X06318 | X06318 | 176970 | GEN-KY  | Protein kinase C, beta 1                                                 | 940  | 804G>A   | S     |
| X06318 | X06318 | 176970 | GEN-KY  | Protein kinase C, beta 1                                                 | 1327 | 1191T>C  | S     |
| X06318 | X06318 | 176970 | GEN-KY  | Protein kinase C, beta 1                                                 | 1906 | 1770C>T  | S     |
| RAF1   | X06409 | 164760 | GEN-19K | Human mRNA fragment for activated c-raf-1 (exons 8-17)                   | 486  | 487T>C   | 3     |
| RAF1   | X06409 | 164760 | GEN-19K | Human mRNA fragment for activated c-raf-1 (exons 8-17)                   | 1947 | 1948C>T  | 3     |
| RAF1   | X06409 | 164760 | GEN-19K | Human mRNA fragment for activated c-raf-1 (exons 8-17)                   | 1992 | 1993C>A  | 3     |
| GSTP1  | X06547 | 134660 | GEN-19N | Human mRNA for class Pi glutathione S-transferase (GST-Pi; E.C.2.5.1.18) | 319  | 313A>G   | I105V |
| GSTP1  | X06547 | 134660 | GEN-19N | Human mRNA for class Pi glutathione S-transferase (GST-Pi; E.C.2.5.1.18) | 347  | 341C>T   | A114V |
| GSTP1  | X06547 | 134660 | GEN-19N | Human mRNA for class Pi glutathione S-transferase (GST-Pi; E.C.2.5.1.18) | 561  | 555C>T   | S     |

|        |        |        |         |                                                             |      |         |       |
|--------|--------|--------|---------|-------------------------------------------------------------|------|---------|-------|
| ITGB1  | X07979 | 135630 | GEN-4E5 | Human mRNA for fibronectin receptor beta subunit            | 1189 | 1086A>C | S     |
| ITGB1  | X07979 | 135630 | GEN-4E5 | Human mRNA for fibronectin receptor beta subunit            | 1279 | 1176A>C | S     |
| ITGB1  | X07979 | 135630 | GEN-4E5 | Human mRNA for fibronectin receptor beta subunit            | 2713 | 2610T>C | 3     |
| ITGB1  | X07979 | 135630 | GEN-4E5 | Human mRNA for fibronectin receptor beta subunit            | 2878 | 2775T>A | 3     |
| ITGB1  | X07979 | 135630 | GEN-4E5 | Human mRNA for fibronectin receptor beta subunit            | 3339 | 3236A>G | 3     |
| ITGB1  | X07979 | 135630 | GEN-4E5 | Human mRNA for fibronectin receptor beta subunit            | 3531 | 3428G>A | 3     |
| ANX5   | X12454 | 131230 | GEN-1M2 | Human mRNA for vascular anticoagulant                       | 128  | (-1)C>T | 5     |
| ANX5   | X12454 | 131230 | GEN-1M2 | Human mRNA for vascular anticoagulant                       | 1413 | 1285T>G | 3     |
| ANX5   | X12454 | 131230 | GEN-1M2 | Human mRNA for vascular anticoagulant                       | 1431 | 1303C>T | 3     |
| ANX5   | X12454 | 131230 | GEN-1M2 | Human mRNA for vascular anticoagulant                       | 1518 | 1390G>A | 3     |
| X12556 | X12556 | 311030 | GEN-1M8 | Human mRNA for dbi proto-oncogene                           | 2670 | 2496T>G | F832L |
| X13589 | X13589 | 107910 | GEN-56  | Cytochrome P450, subfamily XIX (aromatization of androgens) | 364  | 240A>G  | S     |
| X13589 | X13589 | 107910 | GEN-56  | Cytochrome P450, subfamily XIX (aromatization of androgens) | 914  | 790C>T  | R264C |
| X13589 | X13589 | 107910 | GEN-56  | Cytochrome P450, subfamily XIX (aromatization of androgens) | 914  | 790C>T  | R264C |
| X13589 | X13589 | 107910 | GEN-56  | Cytochrome P450, subfamily XIX (aromatization of androgens) | 1655 | 1531C>T | 3     |

|        |        |        |         |                                                                                                  |      |         |       |
|--------|--------|--------|---------|--------------------------------------------------------------------------------------------------|------|---------|-------|
| X13589 | X13589 | 107910 | GEN-56  | subfamily XIX<br>(aromatization of<br>androgens)<br>Cytochrome P450,<br>subfamily XIX            | 1796 | 1672G>T | 3     |
| LIF    | X13967 | 159540 | GEN-1PZ | (aromatization of<br>androgens)<br>Human mRNA for<br>leukaemia inhibitory factor<br>(LIF/HILDA)  | 3710 | 3666T>G | 3     |
| CLU    | X14723 | 185430 | GEN-1SB | Human SP-40,40 mRNA<br>for complement-associated<br>protein SP-40,40 alpha-1<br>and beta-1 chain | 131  | 84C>T   | S     |
| CLU    | X14723 | 185430 | GEN-1SB | Human SP-40,40 mRNA<br>for complement-associated<br>protein SP-40,40 alpha-1<br>and beta-1 chain | 429  | 382G>T  | V128F |
| CLU    | X14723 | 185430 | GEN-1SB | Human SP-40,40 mRNA<br>for complement-associated<br>protein SP-40,40 alpha-1<br>and beta-1 chain | 836  | 789C>T  | S     |
| CLU    | X14723 | 185430 | GEN-1SB | Human SP-40,40 mRNA<br>for complement-associated<br>protein SP-40,40 alpha-1<br>and beta-1 chain | 1234 | 1187C>T | S396L |
| CLU    | X14723 | 185430 | GEN-1SB | Human SP-40,40 mRNA<br>for complement-associated<br>protein SP-40,40 alpha-1<br>and beta-1 chain | 1372 | 1325A>T | Y442F |
| CLU    | X14723 | 185430 | GEN-1SB | Human SP-40,40 mRNA<br>for complement-associated<br>protein SP-40,40 alpha-1<br>and beta-1 chain | 1482 | 1435C>T | 3     |
| CLU    | X14723 | 185430 | GEN-1SB | Human SP-40,40 mRNA<br>for complement-associated<br>protein SP-40,40 alpha-1<br>and beta-1 chain | 1548 | 1501C>T | 3     |
| CLU    | X14723 | 185430 | GEN-1SB | Human SP-40,40 mRNA<br>for complement-associated<br>protein SP-40,40 alpha-1<br>and beta-1 chain | 1645 | 1598A>T | 3     |

|        |        |        |         |                                                                       |      |         |        |
|--------|--------|--------|---------|-----------------------------------------------------------------------|------|---------|--------|
| CSNK2B | X16312 | 115441 | GEN-1XW | and beta-1 chain<br>Human mRNA for<br>phosvitin/casein kinase II      | 271  | 138T>C  | S      |
| CSNK2B | X16312 | 115441 | GEN-1XW | beta subunit<br>Human mRNA for<br>phosvitin/casein kinase II          | 812  | 679A>T  | 3      |
| CSNK2B | X16312 | 115441 | GEN-1XW | beta subunit<br>Human mRNA for<br>phosvitin/casein kinase II          | 885  | 752T>C  | 3      |
| X17033 | X17033 | 192974 | GEN-LG  | beta subunit<br>Integrin, alpha 2 (CD49B,<br>alpha 2 subunit of VLA-2 | 4193 | 4145T>G | 3      |
| X17033 | X17033 | 192974 | GEN-LG  | receptor)<br>Integrin, alpha 2 (CD49B,<br>alpha 2 subunit of VLA-2    | 4849 | 4801A>G | 3      |
| X17033 | X17033 | 192974 | GEN-LG  | receptor)<br>Integrin, alpha 2 (CD49B,<br>alpha 2 subunit of VLA-2    | 4897 | 4849A>G | 3      |
| FGFR1  | X51803 | 136350 | GEN-32G | receptor)<br>Human mRNA for<br>fibroblast growth factor               | 276  | 159T>G  | S      |
| X51841 | X51841 | 147557 | GEN-21  | (FGF) receptor<br>Leukocyte integrin beta-4                           | 4425 | 4299G>A | S      |
| X51841 | X51841 | 147557 | GEN-21  | Leukocyte integrin beta-4                                             | 4437 | 4311G>C | S      |
| X51841 | X51841 | 147557 | GEN-21  | Leukocyte integrin beta-4                                             | 4528 | 4402G>A | A1468T |
| X51841 | X51841 | 147557 | GEN-21  | Leukocyte integrin beta-4                                             | 4821 | 4695C>T | S      |
| X51841 | X51841 | 147557 | GEN-21  | Leukocyte integrin beta-4                                             | 5157 | 5031C>T | S      |
| X51841 | X51841 | 147557 | GEN-21  | Leukocyte integrin beta-4                                             | 5184 | 5058G>A | S      |
| X51841 | X51841 | 147557 | GEN-21  | Leukocyte integrin beta-4                                             | 5252 | 5126C>T | P1709L |
| X51841 | X51841 | 147557 | GEN-21  | Leukocyte integrin beta-4                                             | 5410 | 5284T>C | 3      |
| SPI1   | X52056 | 165170 | GEN-33A | Human mRNA for spi-1<br>proto-oncogene                                | 1328 | 1117C>T | 3      |
| X52425 | X52425 | 147781 | GEN-59  | Interleukin 4 receptor                                                | 3044 | 2869G>A | 3      |
| X52425 | X52425 | 147781 | GEN-59  | Interleukin 4 receptor                                                | 3289 | 3114A>G | 3      |
| X52425 | X52425 | 147781 | GEN-59  | Interleukin 4 receptor                                                | 3391 | 3216C>T | 3      |
| X52479 | X52479 | 176960 | GEN-LM  | Protein kinase C, alpha                                               | 908  | 881A>C  | D294A  |
| FGFR2  | X52832 | 176943 | GEN-341 | Human bek mRNA for<br>fibroblast growth factor<br>receptor-BEK        | 338  | 159A>G  | S      |

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|--------|--------|--------|---------|----------------------------------------------------------------------------------------------------------------------------|------|---------|-------|
| FGFR2  | X52832 | 176943 | GEN-341 | Human bek mRNA for fibroblast growth factor receptor-BEK                                                                   | 2903 | 2724A>T | 3     |
| X54199 | X54199 | 138440 | GEN-LS  | Phosphoribosylglycinamide formyltransferase, phosphoribosylglycinamide synthetase, phosphoribosylaminoimidazole synthetase | 168  | 90G>A   | S     |
| X54315 | X54315 | 114020 | GEN-351 | Human mRNA for N-cadherin                                                                                                  | 2549 | 2448T>C | S     |
| X55005 | X55005 | 190120 | GEN-35S | Human c-erbA-1 mRNA for thyroid hormone receptor                                                                           | 493  | 27A>G   | S     |
| X55005 | X55005 | 190120 | GEN-35S | Human c-erbA-1 mRNA for thyroid hormone receptor alpha                                                                     | 1523 | 1057G>A | V353I |
| X55740 | X55740 | 129190 | GEN-36H | Human placental cDNA coding for 5nucleotidase (EC 3.1.3.5)                                                                 | 3373 | 3324T>G | 3     |
| X57110 | X57110 | 165360 | GEN-MKX | Cas-Br-M (murine) ecotropic retroviral transforming sequence                                                               | 2695 | 2547T>A | S     |
| FGFR4  | X57205 | 134935 | GEN-37M | Human FGFR-4 mRNA for fibroblast growth factor receptor (FGFR-4)                                                           | 83   | 28G>A   | V10I  |
| FGFR4  | X57205 | 134935 | GEN-37M | Human FGFR-4 mRNA for fibroblast growth factor receptor (FGFR-4)                                                           | 217  | 162T>G  | S     |
| GPX3   | X58295 | 138321 | GEN-38S | Human GPx-3 mRNA for plasma glutathione peroxidase                                                                         | 821  | 773C>T  | 3     |
| GPX3   | X58295 | 138321 | GEN-38S | Human GPx-3 mRNA for plasma glutathione peroxidase                                                                         | 979  | 931G>A  | 3     |
| GPX3   | X58295 | 138321 | GEN-38S | Human GPx-3 mRNA for plasma glutathione peroxidase                                                                         | 1187 | 1139T>G | 3     |
| GPX3   | X58295 | 138321 | GEN-38S | Human GPx-3 mRNA for plasma glutathione peroxidase                                                                         | 1354 | 1306C>T | 3     |

|        |        |        |         |                                                    |      |                |      |
|--------|--------|--------|---------|----------------------------------------------------|------|----------------|------|
| GPX3   | X58295 | 138321 | GEN-38S | Human GPx-3 mRNA for plasma glutathione peroxidase | 1443 | 1395C>T        | 3    |
| GPX3   | X58295 | 138321 | GEN-38S | Human GPx-3 mRNA for plasma glutathione peroxidase | 1516 | 1468C>A        | 3    |
| GPX3   | X58295 | 138321 | GEN-38S | Human GPx-3 mRNA for plasma glutathione peroxidase | 1581 | 1533C>T        | 3    |
| X58377 | X58377 | 147681 | GEN-38V | Interleukin 11                                     | 807  | 744A>G         | 3    |
| X58377 | X58377 | 147681 | GEN-38V | Interleukin 11                                     | 927  | 864T>G         | 3    |
| X58377 | X58377 | 147681 | GEN-38V | Interleukin 11                                     | 1964 | 1901T>C        | 3    |
| ITGA6  | X59512 | 147556 | GEN-39W | H.sapiens mRNA for integrin alpha6 subunit         | 186  | 186C>G         | S    |
| ITGA6  | X59512 | 147556 | GEN-39W | H.sapiens mRNA for integrin alpha6 subunit         | 188  | 188G>C         | G63A |
| X59543 | X59543 | 180410 | GEN-M2  | Ribonucleoside diphosphate reductase               | 1037 | 850C>A         | S    |
| X59543 | X59543 | 180410 | GEN-M2  | Ribonucleoside diphosphate reductase               | 2410 | 2223G>A        | S    |
| X59543 | X59543 | 180410 | GEN-M2  | Ribonucleoside diphosphate reductase               | 2410 | 2223G>A        | S    |
| X59543 | X59543 | 180410 | GEN-M2  | Ribonucleoside diphosphate reductase               | 2419 | 2232A>G        | S    |
| X59543 | X59543 | 180410 | GEN-M2  | Ribonucleoside diphosphate reductase               | 2717 | 2530T>A        | 3    |
| X59543 | X59543 | 180410 | GEN-M2  | Ribonucleoside diphosphate reductase               | 2724 | 2537^2538ins T | F    |
| X59543 | X59543 | 180410 | GEN-M2  | Ribonucleoside diphosphate reductase               | 2882 | 2695A>C        | 3    |
| X59618 | X59618 | 180390 | GEN-M3  | Ribonucleotide reductase M2 polypeptide            | 189  | (-6)T>G        | 5    |
| X59618 | X59618 | 180390 | GEN-M3  | Ribonucleotide reductase M2 polypeptide            | 524  | 330C>G         | S    |
| X59618 | X59618 | 180390 | GEN-M3  | Ribonucleotide reductase M2 polypeptide            | 1636 | 1442C>T        | 3    |
| X59618 | X59618 | 180390 | GEN-M3  | Ribonucleotide reductase M2 polypeptide            | 2259 | 2065T>C        | 3    |

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|--------|--------|--------|---------|-----------------------------------------------------------|------|---------|--------|
| NFKB2  | X61498 | 164012 | GEN-3BW | H.sapiens mRNA for NF-kB subunit                          | 2457 | 2294C>T | P765L  |
| KDR    | X61656 | 191306 | GEN-3BZ | H.sapiens mRNA for growth factor receptor tyrosine kinase | 2308 | 2308A>G | T770A  |
| KDR    | X61656 | 191306 | GEN-3BZ | H.sapiens mRNA for growth factor receptor tyrosine kinase | 2353 | 2353G>C | G785R  |
| KDR    | X61656 | 191306 | GEN-3BZ | H.sapiens mRNA for growth factor receptor tyrosine kinase | 2499 | 2499C>G | N833K  |
| KDR    | X61656 | 191306 | GEN-3BZ | H.sapiens mRNA for growth factor receptor tyrosine kinase | 2537 | 2537A>T | E846V  |
| KDR    | X61656 | 191306 | GEN-3BZ | H.sapiens mRNA for growth factor receptor tyrosine kinase | 4123 | 4123G>C | 3      |
| DNMT   | X63692 | 126375 | GEN-3E4 | H.sapiens mRNA for DNA methyltransferase (cytosin-5)-     | 4507 | 4270C>T | R1424C |
| DNMT   | X63692 | 126375 | GEN-3E4 | H.sapiens mRNA for DNA methyltransferase (cytosin-5)-     | 4692 | 4455C>T | S      |
| DNMT   | X63692 | 126375 | GEN-3E4 | H.sapiens mRNA for DNA methyltransferase (cytosin-5)-     | 4922 | 4685C>A | T1562N |
| DNMT   | X63692 | 126375 | GEN-3E4 | H.sapiens mRNA for DNA methyltransferase (cytosin-5)-     | 5235 | 4998C>T | 3      |
| X64177 | X64177 | 156351 | GEN-3EQ | H.sapiens mRNA for metallothionein                        | 63   | 40G>A   | A14T   |
| X64177 | X64177 | 156351 | GEN-3EQ | H.sapiens mRNA for metallothionein                        | 90   | 67A>G   | K23E   |
| X64177 | X64177 | 156351 | GEN-3EQ | H.sapiens mRNA for metallothionein                        | 125  | 102C>T  | S      |
| X64177 | X64177 | 156351 | GEN-3EQ | H.sapiens mRNA for metallothionein                        | 131  | 108T>C  | S      |
| X64177 | X64177 | 156351 | GEN-3EQ | H.sapiens mRNA for metallothionein                        | 168  | 145A>G  | I49V   |
| X64177 | X64177 | 156351 | GEN-3EQ | H.sapiens mRNA for metallothionein                        | 182  | 159G>A  | S      |

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|        |        |        |         |                                                                                     |      |         |       |
|--------|--------|--------|---------|-------------------------------------------------------------------------------------|------|---------|-------|
| X65019 | X65019 | 147678 | GEN-6G  | INTERLEUKIN 1 BETA<br>CONVERTASE<br>PRECURSOR                                       | 51   | 44G>A   | R15H  |
| X65019 | X65019 | 147678 | GEN-6G  | INTERLEUKIN 1 BETA<br>CONVERTASE<br>PRECURSOR                                       | 116  | 109A>C  | K37Q  |
| X65019 | X65019 | 147678 | GEN-6G  | INTERLEUKIN 1 BETA<br>CONVERTASE<br>PRECURSOR                                       | 261  | 254G>A  | G85E  |
| X66364 | X66364 | 123831 | GEN-3GM | H.sapiens mRNA<br>PSSALRE for<br>serine/threonine protein<br>kinase                 | 495  | 471T>G  | C157W |
| NTRK1  | X66397 | 191315 | GEN-3GN | H.sapiens tpr mRNA                                                                  | 2632 | 2335G>A | V779I |
| X69141 | X69141 | 184420 | GEN-3J9 | H.sapiens mRNA for<br>squalene synthase                                             | 112  | 21T>C   | S     |
| X69141 | X69141 | 184420 | GEN-3J9 | H.sapiens mRNA for<br>squalene synthase                                             | 292  | 201C>T  | S     |
| X69141 | X69141 | 184420 | GEN-3J9 | H.sapiens mRNA for<br>squalene synthase                                             | 1436 | 1345T>C | 3     |
| X69141 | X69141 | 184420 | GEN-3J9 | H.sapiens mRNA for<br>squalene synthase                                             | 1579 | 1488T>C | 3     |
| X69141 | X69141 | 184420 | GEN-3J9 | H.sapiens mRNA for<br>squalene synthase                                             | 1621 | 1530C>T | 3     |
| X69141 | X69141 | 184420 | GEN-3J9 | H.sapiens mRNA for<br>squalene synthase                                             | 1719 | 1628A>C | 3     |
| X69141 | X69141 | 184420 | GEN-3J9 | H.sapiens mRNA for<br>squalene synthase                                             | 1904 | 1813G>C | 3     |
| GPX4   | X71973 | 138322 | GEN-3L1 | H.sapiens GPX-4 mRNA<br>for phospholipid<br>hydroperoxide glutathione<br>peroxidase | 718  | 638T>C  | 3     |
| GPX4   | X71973 | 138322 | GEN-3L1 | H.sapiens GPX-4 mRNA<br>for phospholipid<br>hydroperoxide glutathione<br>peroxidase | 837  | 757C>A  | 3     |
| GPX4   | X71973 | 138322 | GEN-3L1 | H.sapiens GPX-4 mRNA<br>for phospholipid<br>hydroperoxide glutathione<br>peroxidase | 882  | 802A>C  | 3     |

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|        |        |        |         |                                                                      |      |          |        |
|--------|--------|--------|---------|----------------------------------------------------------------------|------|----------|--------|
| X75958 | X75958 | 600456 | GEN-3OE | H.sapiens trkB mRNA for protein-tyrosine kinase                      | 30   | (-68)C>G | 5      |
| X75958 | X75958 | 600456 | GEN-3OE | H.sapiens trkB mRNA for protein-tyrosine kinase                      | 2010 | 1913A>G  | 3      |
| X75958 | X75958 | 600456 | GEN-3OE | H.sapiens trkB mRNA for protein-tyrosine kinase                      | 2101 | 2004C>T  | 3      |
| X75962 | X75962 | 600315 | GEN-MNA | H.sapiens mRNA for OX40 homologue                                    | 836  | 831C>T   | S      |
| X76061 | X76061 | 180203 | GEN-3OK | H.sapiens p130 mRNA for 130K protein                                 | 685  | 616G>A   | V206M  |
| X76061 | X76061 | 180203 | GEN-3OK | H.sapiens p130 mRNA for 130K protein                                 | 2659 | 2590T>C  | S      |
| X76061 | X76061 | 180203 | GEN-3OK | H.sapiens p130 mRNA for 130K protein                                 | 3585 | 3516G>C  | 3      |
| X76104 | X76104 | 600831 | GEN-3OO | H.sapiens DAP-kinase mRNA                                            | 4376 | 4040A>G  | N1347S |
| X76105 | X76105 | 600954 | GEN-3ON | H.sapiens DAP-1 mRNA                                                 | 887  | 728C>T   | 3      |
| X76105 | X76105 | 600954 | GEN-3ON | H.sapiens DAP-1 mRNA                                                 | 1089 | 930A>G   | 3      |
| X76105 | X76105 | 600954 | GEN-3ON | H.sapiens DAP-1 mRNA                                                 | 1890 | 1731A>G  | 3      |
| X77722 | X77722 | 602376 | GEN-29  | Interferon (alpha,beta, omega) receptor 2 (splice variant)           | 253  | 28G>T    | V10F   |
| X77722 | X77722 | 602376 | GEN-29  | Interferon (alpha,beta, omega) receptor 2 (splice variant)           | 1128 | 903A>G   | S      |
| X77794 | X77794 | 601578 | GEN-N8  | Cyclin G1                                                            | 1133 | 1013G>A  | 3      |
| X79389 | X79389 | 600436 | GEN-3T7 | H.sapiens GSTT1 mRNA                                                 | 824  | 824T>C   | 3      |
| X79483 | X79483 | 602399 | GEN-LPR | H.sapiens ERK6 mRNA for extracellular signal regulated kinase        | 1287 | 1254T>G  | 3      |
| X80230 | X80230 | 603251 | GEN-3UM | H.sapiens mRNA (clone C-2k) mRNA for serine/threonine protein kinase | 25   | (-74)C>T | 5      |
| X80230 | X80230 | 603251 | GEN-3UM | H.sapiens mRNA (clone C-2k) mRNA for serine/threonine protein kinase | 77   | (-22)C>T | 5      |

|        |        |        |         |                                                                      |      |           |       |
|--------|--------|--------|---------|----------------------------------------------------------------------|------|-----------|-------|
| X80230 | X80230 | 603251 | GEN-3UM | H.sapiens mRNA (clone C-2k) mRNA for serine/threonine protein kinase | 1516 | 1418G>A   | 3     |
| X80230 | X80230 | 603251 | GEN-3UM | H.sapiens mRNA (clone C-2k) mRNA for serine/threonine protein kinase | 1574 | 1476A>G   | 3     |
| X83544 | X83544 | 602074 | GEN-3Y6 | H.sapiens DAP-3 mRNA                                                 | 41   | (-33)G>T  | 5     |
| X83544 | X83544 | 602074 | GEN-3Y6 | H.sapiens DAP-3 mRNA                                                 | 285  | 212C>T    | S71F  |
| X83544 | X83544 | 602074 | GEN-3Y6 | H.sapiens DAP-3 mRNA                                                 | 294  | 221A>G    | D74G  |
| X83544 | X83544 | 602074 | GEN-3Y6 | H.sapiens DAP-3 mRNA                                                 | 877  | 804T>C    | S     |
| X83544 | X83544 | 602074 | GEN-3Y6 | H.sapiens DAP-3 mRNA                                                 | 1106 | 1033G>A   | V345I |
| X83861 | X83861 | 176806 | GEN-5H  | Prostaglandin E receptor 3 (subtype EP3) {alternative products}      | 387  | 180C>G    | S     |
| X84213 | X84213 | 600516 | GEN-3ZC | H.sapiens BAK mRNA for BCI-2 homologue                               | 32   | (-161)C>T | 5     |
| X84213 | X84213 | 600516 | GEN-3ZC | H.sapiens BAK mRNA for BCI-2 homologue                               | 317  | 125G>A    | R42H  |
| X84213 | X84213 | 600516 | GEN-3ZC | H.sapiens BAK mRNA for BCI-2 homologue                               | 435  | 243C>T    | S     |
| X84213 | X84213 | 600516 | GEN-3ZC | H.sapiens BAK mRNA for BCI-2 homologue                               | 616  | 424G>A    | V142I |
| X84213 | X84213 | 600516 | GEN-3ZC | H.sapiens BAK mRNA for BCI-2 homologue                               | 663  | 471C>T    | S     |
| X84213 | X84213 | 600516 | GEN-3ZC | H.sapiens BAK mRNA for BCI-2 homologue                               | 900  | 708T>C    | 3     |
| X84213 | X84213 | 600516 | GEN-3ZC | H.sapiens BAK mRNA for BCI-2 homologue                               | 974  | 782C>T    | 3     |
| X86681 | X86681 | 602110 | GEN-41E | H.sapiens mRNA for nucleolar protein, HNP36                          | 1725 | 1340G>A   | 3     |
| X90858 | X90858 | 191730 | GEN-NQ  | Uridine phosphorylase                                                | 309  | (-44)C>T  | 5     |
| X90858 | X90858 | 191730 | GEN-NQ  | Uridine phosphorylase                                                | 824  | 472G>A    | A158T |
| X92106 | X92106 | 602403 | GEN-    | H.sapiens mRNA for                                                   | 1405 | 1327A>G   | I443V |

|        |        |        |                |                                                                      |      |         |        |
|--------|--------|--------|----------------|----------------------------------------------------------------------|------|---------|--------|
| X96395 | X96395 | 601107 | 47S<br>GEN-4AM | bleomycin hydrolase                                                  | 848  | 811G>T  | A271S  |
| Y00285 | Y00285 | 147280 | GEN-6I         | H.sapiens mRNA for canalicular multidrug resistance protein          | 4613 | 446G>A  | S1489N |
| Y00285 | Y00285 | 147280 | GEN-6I         | IGF-2 receptor                                                       | 6371 | 6224C>T | T2075M |
| Y00285 | Y00285 | 147280 | GEN-6I         | IGF-2 receptor                                                       | 6813 | 666C>T  | S      |
| Y00285 | Y00285 | 147280 | GEN-6I         | IGF-2 receptor                                                       | 7150 | 7003G>A | V2335M |
| Y00285 | Y00285 | 147280 | GEN-6I         | IGF-2 receptor                                                       | 8685 | 8538C>A | 3      |
| GPX1   | Y00433 | 138320 | GEN-TJ         | Human mRNA for glutathione peroxidase (EC 1.11.1.9.)                 | 504  | 186G>A  | S      |
| GPX1   | Y00433 | 138320 | GEN-TJ         | Human mRNA for glutathione peroxidase (EC 1.11.1.9.)                 | 610  | 292C>G  | R98G   |
| GPX1   | Y00433 | 138320 | GEN-TJ         | Human mRNA for glutathione peroxidase (EC 1.11.1.9.)                 | 911  | 593C>T  | P198L  |
| GPX1   | Y00433 | 138320 | GEN-TJ         | Human mRNA for glutathione peroxidase (EC 1.11.1.9.)                 | 1048 | 730A>C  | 3      |
| GPX1   | Y00433 | 138320 | GEN-TJ         | Human mRNA for glutathione peroxidase (EC 1.11.1.9.)                 | 1110 | 792A>C  | 3      |
| Y00486 | Y00486 | 102600 | GEN-MGW        | Human APRT gene for adenine phosphoribosyltransferase                | 503  | 432C>A  | S      |
| Y00486 | Y00486 | 102600 | GEN-MGW        | Human APRT gene for adenine phosphoribosyltransferase                | 505  | 434G>C  | R145P  |
| Y00486 | Y00486 | 102600 | GEN-MGW        | Human APRT gene for adenine phosphoribosyltransferase                | 792  | 721A>G  | 3      |
| PAI2   | Y00630 | 173390 | GEN-U6         | Human mRNA for Arg-Serpin (plasminogen activator-inhibitor 2, PAI-2) | 430  | 358A>G  | N120D  |
| PAI2   | Y00630 | 173390 | GEN-U6         | Human mRNA for Arg-Serpin (plasminogen activator-inhibitor 2, PAI-2) | 1251 | 1179T>G | S      |
| PAI2   | Y00630 | 173390 | GEN-U6         | Human mRNA for Arg-Serpin (plasminogen activator-inhibitor 2, PAI-2) | 1762 | 1690G>A | 3      |

|        |        |        |         |                                                                       |      |         |       |
|--------|--------|--------|---------|-----------------------------------------------------------------------|------|---------|-------|
| OAT    | Y07511 | 258870 | GEN-1E3 | Serpin (plasminogen activator-inhibitor 2, PAI-2)                     | 1174 | 1134C>T | S     |
| OAT    | Y07511 | 258870 | GEN-1E3 | Human mRNA for kidney ornithine aminotransferase (EC 2.6.1.13)        | 1545 | 1505C>T | 3     |
| Y08200 | Y08200 | 601905 | GEN-1FT | Human mRNA for kidney ornithine aminotransferase (EC 2.6.1.13)        | 1696 | 1422C>T | S     |
| Y08201 | Y08201 | 179080 | GEN-9B  | Homo sapiens mRNA for rab geranylgeranyl transferase, alpha-subunit   | 54   | 51T>A   | S     |
| Y10659 | Y10659 | 300119 | GEN-1J6 | Geranylgeranyl transferase type II beta-subunit                       | 1116 | 1073G>A | G358D |
| Z11695 | Z11695 | 176948 | GEN-1L1 | H.sapiens IL-13Ra mRNA                                                | 1287 | 1153G>A | 3     |
| Z11696 | Z11696 | 601795 | GEN-1L0 | H.sapiens 40 kDa protein kinase related to rat ERK2                   | 449  | 449T>G  | I150S |
| Z14138 | Z14138 | 603259 | GEN-1QS | H.sapiens 44kDa protein kinase related to rat ERK1                    | 394  | 234T>C  | S     |
|        |        |        |         | H.sapiens (Ewings sarcoma cell line) mRNA encoding open reading frame |      |         |       |
| Z15108 | Z15108 | 176982 | GEN-1TE | H.sapiens mRNA for protein kinase C zeta                              | 246  | 240T>C  | S     |
| Z15108 | Z15108 | 176982 | GEN-1TE | H.sapiens mRNA for protein kinase C zeta                              | 1694 | 1688A>C | D563A |
| Z15108 | Z15108 | 176982 | GEN-1TE | H.sapiens mRNA for protein kinase C zeta                              | 2033 | 2027G>A | 3     |
| Z15108 | Z15108 | 176982 | GEN-1TE | H.sapiens mRNA for protein kinase C zeta                              | 2086 | 2080T>G | 3     |
| Z35491 | Z35491 | 601497 | GEN-2ME | H.sapiens mRNA for novel glucocorticoid receptor-associated protein   | 315  | 37G>A   | E13K  |
| Z35491 | Z35491 | 601497 | GEN-2ME | H.sapiens mRNA for novel glucocorticoid receptor-associated protein   | 333  | 55G>A   | E19K  |
| Z35491 | Z35491 | 601497 | GEN-2ME | H.sapiens mRNA for novel glucocorticoid receptor-associated protein   | 1297 | 1019A>C | 3     |
| CCNF   | Z36714 | 600227 | GEN-2NB | H.sapiens mRNA for cyclin F                                           | 4062 | 4019C>A | 3     |

Z48810 Z48810 602664 GEN- 1280 1239A>C 3

H.sapiens mRNA for TX  
protease precursor

Table 13.  
Identified  
Variances  
In Genes  
for  
Pathways  
Identified  
in  
Neurologi  
cal and  
Psychiatri  
c  
Diseases

|                                                                                                          |         |        |         |              |       |
|----------------------------------------------------------------------------------------------------------|---------|--------|---------|--------------|-------|
| AB00026                                                                                                  | AB00026 | 602784 | GEN-16N | 215 210T>C   | S     |
| 3                                                                                                        | 3       |        |         |              |       |
| Human mRNA for prepro cortistatin like peptide, complete cds                                             |         |        |         |              |       |
| AB00063                                                                                                  | AB00063 | 601646 | GEN-169 | 1423 1409T>C | L470P |
| 4                                                                                                        | 4       |        |         |              |       |
| Homo sapiens mRNA for protein phosphatase 2A delta (B) regulatory subunit, delta 1 isoform, complete cds |         |        |         |              |       |
| AB00063                                                                                                  | AB00063 | 601646 | GEN-169 | 2163 2149T>A | 3     |
| 4                                                                                                        | 4       |        |         |              |       |
| Homo sapiens mRNA for protein phosphatase 2A delta (B) regulatory subunit, delta 1 isoform, complete cds |         |        |         |              |       |
| AB00234                                                                                                  | AB00234 | 601581 | GEN-1CR | 2562 2148G>C | S     |
| 1                                                                                                        | 1       |        |         |              |       |
| Human mRNA for KIAA0343 gene, complete cds                                                               |         |        |         |              |       |
| AB00255                                                                                                  | AB00255 | 601717 | GEN-1AA | 1467 1443T>C | S     |
| 9                                                                                                        | 9       |        |         |              |       |
| hunc18b2, complete cds                                                                                   |         |        |         |              |       |
| AB00255                                                                                                  | AB00255 | 601717 | GEN-1AA | 1600 1576G>A | V526I |
| 9                                                                                                        | 9       |        |         |              |       |
| hunc18b2, complete cds                                                                                   |         |        |         |              |       |
| AB00255                                                                                                  | AB00255 | 601717 | GEN-1AA | 1669 1645G>A | A549T |
| 9                                                                                                        | 9       |        |         |              |       |
| hunc18b2, complete cds                                                                                   |         |        |         |              |       |
| AB00591                                                                                                  | AB00591 | 602758 | GEN-VC  | 891 822C>T   | S     |
| 0                                                                                                        | 0       |        |         |              |       |
| Homo sapiens mRNA for phosphatidylinositol 4-                                                            |         |        |         |              |       |

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|          |          |        |         |                                                                       |              |       |
|----------|----------|--------|---------|-----------------------------------------------------------------------|--------------|-------|
| AB01071  | AB01071  | 602601 | GEN-1SQ | kinase, complete cds                                                  | 1071 1010T>A | 3     |
|          | 0        | 0      |         | Homo sapiens mRNA for lectin-like oxidized LDL receptor, complete cds |              |       |
| AB01071  | AB01071  | 602601 | GEN-1SQ | Homo sapiens mRNA for lectin-like oxidized LDL receptor, complete cds | 1073 1012T>C | 3     |
|          | 0        | 0      |         |                                                                       |              |       |
| AB01071  | AB01071  | 602601 | GEN-1SQ | Homo sapiens mRNA for lectin-like oxidized LDL receptor, complete cds | 1073 1012T>C | 3     |
|          | 0        | 0      |         |                                                                       |              |       |
| AB01071  | AB01071  | 602601 | GEN-1SQ | Homo sapiens mRNA for lectin-like oxidized LDL receptor, complete cds | 1801 1740A>G | 3     |
|          | 0        | 0      |         |                                                                       |              |       |
| AB01071  | AB01071  | 602601 | GEN-1SQ | Homo sapiens mRNA for lectin-like oxidized LDL receptor, complete cds | 2199 2138G>A | 3     |
|          | 0        | 0      |         |                                                                       |              |       |
| AB01388  | AB01388  | 603208 | GEN-CBP | Inward rectifier potassium channel Kir 1.4                            | 1469 1218A>G | 3     |
| AB01531  | AB01531  | None   | GEN-L2T | Homo sapiens mRNA for gamma2-adaptin, complete cds                    | 377 332A>G   | D111G |
|          | 8        | 8      |         |                                                                       |              |       |
| AB01531  | AB01531  | None   | GEN-L2T | Homo sapiens mRNA for gamma2-adaptin, complete cds                    | 534 489G>A   | S     |
|          | 8        | 8      |         |                                                                       |              |       |
| AB01531  | AB01531  | None   | GEN-L2T | Homo sapiens mRNA for gamma2-adaptin, complete cds                    | 2444 2399C>A | 3     |
|          | 8        | 8      |         |                                                                       |              |       |
| AF000234 | AF000234 | 600846 | GEN-16J | PURINERGIC RECEPTOR P2X, LIGAND-GATED ION CHANNEL, 4; P2RX4           | 365 365C>T   | P122L |
| AF000234 | AF000234 | 600846 | GEN-16J | PURINERGIC RECEPTOR P2X, LIGAND-GATED ION CHANNEL, 4; P2RX4           | 381 381G>A   | S     |
| AF000234 | AF000234 | 600846 | GEN-16J | PURINERGIC RECEPTOR P2X, LIGAND-GATED ION CHANNEL, 4; P2RX4           | 624 624A>G   | S     |
| AF000234 | AF000234 | 600846 | GEN-16J | PURINERGIC RECEPTOR P2X, LIGAND-GATED ION CHANNEL, 4; P2RX4           | 641 641C>T   | P214L |
| AF000234 | AF000234 | 600846 | GEN-16J | PURINERGIC RECEPTOR P2X, LIGAND-GATED ION CHANNEL, 4; P2RX4           | 1161 1161T>C | 3     |

|          |          |        |             |                                                                                          |              |       |
|----------|----------|--------|-------------|------------------------------------------------------------------------------------------|--------------|-------|
| AF004562 | AF004562 | 602926 | GEN-UK      | CHANNEL, 4; P2RX4<br>Homo sapiens hUNC18a<br>alternatively-spliced<br>mRNA, complete cds | 1830 1710A>T | S     |
| AF004562 | AF004562 | 602926 | GEN-UK      | Homo sapiens hUNC18a<br>alternatively-spliced<br>mRNA, complete cds                      | 3322 3202T>C | 3     |
| AF004562 | AF004562 | 602926 | GEN-UK      | Homo sapiens hUNC18a<br>alternatively-spliced<br>mRNA, complete cds                      | 3673 3553C>G | 3     |
| AF006823 | AF006823 | 603220 | GEN-WS      | Homo sapiens TWIK-<br>related acid-sensitive K+<br>channel (TASK) mRNA,<br>complete cds  | 1160 1035G>A | S     |
| AF007548 | AF007548 | None   | GEN-<br>12G | Homo sapiens golgi<br>SNARE (GS27) mRNA,<br>complete cds                                 | 200 200G>A   | R67K  |
| AF010126 | AF010126 | 602998 | GEN-<br>1SR | Homo sapiens breast<br>cancer-specific protein 1<br>(BCSG1) mRNA, complete<br>cds        | 206 195C>G   | S     |
| AF010126 | AF010126 | 602998 | GEN-<br>1SR | Homo sapiens breast<br>cancer-specific protein 1<br>(BCSG1) mRNA, complete<br>cds        | 340 329A>T   | E110V |
| AF010126 | AF010126 | 602998 | GEN-<br>1SR | Homo sapiens breast<br>cancer-specific protein 1<br>(BCSG1) mRNA, complete<br>cds        | 518 507C>T   | 3     |
| AF016709 | AF016709 | 602836 | GEN-<br>1NE | PURINERGIC RECEPTOR<br>P2X, LIGAND-GATED ION<br>CHANNEL, 5; P2RX5                        | 1023 987T>C  | S     |
| AF016709 | AF016709 | 602836 | GEN-<br>1NE | PURINERGIC RECEPTOR<br>P2X, LIGAND-GATED ION<br>CHANNEL, 5; P2RX5                        | 1025 989T>C  | F330S |
| AF016709 | AF016709 | 602836 | GEN-<br>1NE | PURINERGIC RECEPTOR<br>P2X, LIGAND-GATED ION<br>CHANNEL, 5; P2RX5                        | 1090 1054G>C | E352Q |
| AF016709 | AF016709 | 602836 | GEN-<br>1NE | PURINERGIC RECEPTOR<br>P2X, LIGAND-GATED ION<br>CHANNEL, 5; P2RX5                        | 1321 1285G>A | 3     |

|          |          |        |         |                                                                            |              |       |
|----------|----------|--------|---------|----------------------------------------------------------------------------|--------------|-------|
| AF016709 | AF016709 | 602836 | GEN-1NE | PURINERGIC RECEPTOR P2X, LIGAND-GATED ION CHANNEL, 5; P2RX5                | 1424 1388C>G | 3     |
| AF016709 | AF016709 | 602836 | GEN-1NE | PURINERGIC RECEPTOR P2X, LIGAND-GATED ION CHANNEL, 5; P2RX5                | 1512 1476G>A | 3     |
| AF016709 | AF016709 | 602836 | GEN-1NE | PURINERGIC RECEPTOR P2X, LIGAND-GATED ION CHANNEL, 5; P2RX5                | 1743 1707A>G | 3     |
| AF016709 | AF016709 | 602836 | GEN-1NE | PURINERGIC RECEPTOR P2X, LIGAND-GATED ION CHANNEL, 5; P2RX5                | 1858 1822A>G | 3     |
| AF016903 | AF016903 | None   | GEN-1M7 | Homo sapiens agrin precursor mRNA, partial cds                             | 516 516C>G   | S     |
| AF016903 | AF016903 | None   | GEN-1M7 | Homo sapiens agrin precursor mRNA, partial cds                             | 518 518G>C   | R173P |
| AF016903 | AF016903 | None   | GEN-1M7 | Homo sapiens agrin precursor mRNA, partial cds                             | 3501 3501C>T | S     |
| AF016903 | AF016903 | None   | GEN-1M7 | Homo sapiens agrin precursor mRNA, partial cds                             | 6422 6422A>G | 3     |
| AF016903 | AF016903 | None   | GEN-1M7 | Homo sapiens agrin precursor mRNA, partial cds                             | 6704 6704A>G | 3     |
| HRH1     | AF026261 | 600167 | GEN-26W | Histamine receptor H1                                                      | 1068 1068A>G | S     |
| AVPR1B   | AF030512 | 600264 | GEN-4FF | Homo sapiens small cell vasopressin subtype 1b receptor mRNA, complete cds | 273 150G>A   | S     |
| AF030625 | AF030625 | 600821 | GEN-2   | Vasopressin V1A receptor                                                   | 314 291C>T   | S     |
| AF030625 | AF030625 | 600821 | GEN-2   | Vasopressin V1A receptor                                                   | 431 408T>C   | S     |
| AF030625 | AF030625 | 600821 | GEN-2   | Vasopressin V1A receptor                                                   | 506 483A>G   | S     |
| AF033382 | AF033382 | 603787 | GEN-2OT | potassium channel                                                          | 476 476G>T   | G159V |
| AF033382 | AF033382 | 603787 | GEN-2OT | potassium channel                                                          | 1083 1083C>T | S     |
| AF034795 | AF034795 | 116935 | GEN-    | Homo sapiens cell matrix                                                   | 1404 853G>A  | 3     |

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|          |          |        |         |                                                                                           |              |       |
|----------|----------|--------|---------|-------------------------------------------------------------------------------------------|--------------|-------|
| AF034795 | AF034795 | 116935 | 2GB     | adhesion regulator variant (CMAR) mRNA, complete cds                                      | 1411 860C>T  | 3     |
| AF034795 | AF034795 | 116935 | GEN-2GB | Homo sapiens cell matrix adhesion regulator variant (CMAR) mRNA, complete cds             | 1811 1260G>A | 3     |
| TUBB     | AF035316 | 191130 | GEN-2IH | Homo sapiens clone 23678 mRNA, partial cds                                                | 273 273G>A   | F     |
| TUBB     | AF035316 | 191130 | GEN-2IH | Homo sapiens clone 23678 mRNA, partial cds                                                | 295 295G>C   | A99P  |
| TUBB     | AF035316 | 191130 | GEN-2IH | Homo sapiens clone 23678 mRNA, partial cds                                                | 302 302C>T   | T101I |
| TUBB     | AF035316 | 191130 | GEN-2IH | Homo sapiens clone 23678 mRNA, partial cds                                                | 1059 1059G>A | 3     |
| AF036892 | AF036892 | 601937 | GEN-7W  | Nuclear receptor coactivator (ACTR)                                                       | 842 659G>T   | R220I |
| AF036892 | AF036892 | 601937 | GEN-7W  | Nuclear receptor coactivator (ACTR)                                                       | 1971 1788G>C | Q596H |
| AF036892 | AF036892 | 601937 | GEN-7W  | Nuclear receptor coactivator (ACTR)                                                       | 3048 2865A>G | S     |
| AF036892 | AF036892 | 601937 | GEN-7W  | Nuclear receptor coactivator (ACTR)                                                       | 3909 3726A>G | S     |
| AF036892 | AF036892 | 601937 | GEN-7W  | Nuclear receptor coactivator (ACTR)                                                       | 4483 4300T>C | 3     |
| AF036892 | AF036892 | 601937 | GEN-7W  | Nuclear receptor coactivator (ACTR)                                                       | 5644 5461A>G | 3     |
| AF036892 | AF036892 | 601937 | GEN-7W  | Nuclear receptor coactivator (ACTR)                                                       | 5675 5492T>A | 3     |
| AF036892 | AF036892 | 601937 | GEN-7W  | Nuclear receptor coactivator (ACTR)                                                       | 6051 5868T>G | 3     |
| AF036892 | AF036892 | 601937 | GEN-7W  | Nuclear receptor coactivator (ACTR)                                                       | 6664 6481G>A | 3     |
| AF038173 | AF038173 | 601255 | GEN-2QH | Homo sapiens clone 23723 axonal transporter of synaptic vesicles (ATSV) mRNA, partial cds | 1368 1368T>C | 3     |

|          |          |        |             |                                                                                                              |                |       |
|----------|----------|--------|-------------|--------------------------------------------------------------------------------------------------------------|----------------|-------|
| AF038173 | AF038173 | 601255 | GEN-<br>2QH | Homo sapiens clone 23723<br>axonal transporter of<br>synaptic vesicles (ATSV)<br>mRNA, partial cds           | 1387 1387A>G   | 3     |
| AF038173 | AF038173 | 601255 | GEN-<br>2QH | Homo sapiens clone 23723<br>axonal transporter of<br>synaptic vesicles (ATSV)<br>mRNA, partial cds           | 1501 1501G>C   | 3     |
| AF039400 | AF039400 | 603906 | GEN-<br>MQY | Homo sapiens calcium-<br>dependent chloride<br>channel-1 (hCLCA1)<br>mRNA, complete cds                      | 2787 2436T>C   | S     |
| AF043472 | AF043472 | 603888 | GEN-<br>2XX | Homo sapiens Shab-<br>related delayed-rectifier K+<br>channel alpha subunit<br>(KCNK3) mRNA, complete<br>cds | 1840 1709T>G   | 3     |
| AF043473 | AF043473 | 602905 | GEN-<br>2XW | POTASSIUM CHANNEL<br>PROTEIN KV2.1                                                                           | 1308 1308G>T   | S     |
| AF046873 | AF046873 | 602705 | GEN-<br>LFF | Homo sapiens synapsin<br>IIIa mRNA, complete cds                                                             | 1364 1328G>A   | R443H |
| AF047442 | AF047442 | None   | GEN-<br>LFO | Homo sapiens vesicle<br>trafficking protein sec22b<br>mRNA, complete cds                                     | 160 96G>A      | S     |
| AF048837 | AF048837 | 602973 | GEN-<br>LGG | Homo sapiens cGMP-<br>specific phosphodiesterase<br>(PDE9A2) mRNA,<br>complete cds                           | 1551 1491T>C   | S     |
| AF052224 | AF052224 | None   | GEN-<br>MR1 | Homo sapiens neuronal<br>double zinc finger protein<br>(ZNF231) mRNA, complete<br>cds                        | 15480 15365T>G | 3     |
| AF052224 | AF052224 | None   | GEN-<br>MR1 | Homo sapiens neuronal<br>double zinc finger protein<br>(ZNF231) mRNA, complete<br>cds                        | 15560 15445C>T | 3     |
| AF052224 | AF052224 | None   | GEN-<br>MR1 | Homo sapiens neuronal<br>double zinc finger protein<br>(ZNF231) mRNA, complete<br>cds                        | 15745 15630C>T | 3     |
| AF053233 | AF053233 | None   | GEN-        | Homo sapiens endobrevin<br>cds                                                                               | 225 201A>G     | S     |

|          |          |        |                    |                                                                                                           |              |        |
|----------|----------|--------|--------------------|-----------------------------------------------------------------------------------------------------------|--------------|--------|
| AF058921 | AF058921 | None   | 38F<br>GEN-<br>LJY | mRNA, complete cds<br>Homo sapiens cytosolic<br>phospholipase A2-gamma<br>mRNA, complete cds              | 1972 1663G>A | 3      |
| AF058921 | AF058921 | None   | GEN-<br>LJY        | Homo sapiens cytosolic<br>phospholipase A2-gamma<br>mRNA, complete cds                                    | 1989 1680A>T | 3      |
| AF060538 | AF060538 | 185880 | GEN-LL4            | Homo sapiens vesicle<br>associated membrane<br>protein-1B mRNA,<br>alternatively spliced,<br>complete cds | 780 650C>T   | 3      |
| AF064548 | AF064548 | 603506 | GEN-<br>KV4        | Homo sapiens low-density<br>lipoprotein receptor-related<br>protein 5 (LRP5) mRNA,<br>complete cds        | 1695 1647C>T | S      |
| AF064548 | AF064548 | 603506 | GEN-<br>KV4        | Homo sapiens low-density<br>lipoprotein receptor-related<br>protein 5 (LRP5) mRNA,<br>complete cds        | 4037 3989C>T | A1330V |
| AF064548 | AF064548 | 603506 | GEN-<br>KV4        | Homo sapiens low-density<br>lipoprotein receptor-related<br>protein 5 (LRP5) mRNA,<br>complete cds        | 4683 4635C>A | S      |
| AF064548 | AF064548 | 603506 | GEN-<br>KV4        | Homo sapiens low-density<br>lipoprotein receptor-related<br>protein 5 (LRP5) mRNA,<br>complete cds        | 4802 4754C>T | S1585L |
| AF077671 | AF077671 | 600755 | GEN-<br>LMT        | Homo sapiens synapsin IIa<br>(SYN2) mRNA, complete<br>cds                                                 | 1246 1225T>C | S      |
| AJ130763 | AJ130763 | 254780 | GEN-<br>LDP        | Homo sapiens mRNA for<br>LAFPTase, isoform 1,<br>partial                                                  | 161 159G>A   | S      |
| AJ130763 | AJ130763 | 254780 | GEN-<br>LDP        | Homo sapiens mRNA for<br>LAFPTase, isoform 1,<br>partial                                                  | 287 285T>A   | S      |
| D12614   | D12614   | 153440 | GEN-QD             | Human mRNA for<br>lymphotoxin (TNF-beta),<br>complete cds                                                 | 319 179C>A   | T60N   |
| D13388   | D13388   | 602837 | GEN-A7             | DNAJ PROTEIN                                                                                              | 207 90C>T    | S      |

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|---------|--------|--------|---------|--------------------------------------------------------------------------|--------------|-------|
| CYP11B2 | D13752 | 124080 | GEN-CCD | HOMOLOG 2<br>Human CYP11B2 gene for steroid 18-hydroxylase, complete cds | 1600 1593G>A | 3     |
| D13811  | D13811 | 238310 | GEN-AA  | Glycine cleavage system: Protein T                                       | 277 148G>T   | V50L  |
| D13811  | D13811 | 238310 | GEN-AA  | Glycine cleavage system: Protein T                                       | 1073 944G>A  | R315K |
| D13811  | D13811 | 238310 | GEN-AA  | Glycine cleavage system: Protein T                                       | 1083 954G>A  | S     |
| D13811  | D13811 | 238310 | GEN-AA  | Glycine cleavage system: Protein T                                       | 1773 1644C>T | 3     |
| D13811  | D13811 | 238310 | GEN-AA  | Glycine cleavage system: Protein T                                       | 2037 1908C>T | 3     |
| D16469  | D16469 | 300197 | GEN-1Y2 | Human mRNA for ORF, Xq terminal portion                                  | 2294 941A>G  | 3     |
| D16469  | D16469 | 300197 | GEN-1Y2 | Human mRNA for ORF, Xq terminal portion                                  | 2460 1107A>G | 3     |
| D16469  | D16469 | 300197 | GEN-1Y2 | Human mRNA for ORF, Xq terminal portion                                  | 2660 1307C>A | 3     |
| D25235  | D25235 | 104221 | GEN-3   | Adrenergic receptor alpha 1c                                             | 1035 599T>G  | I200S |
| D25235  | D25235 | 104221 | GEN-3   | Adrenergic receptor alpha 1c                                             | 1475 1039C>T | R347C |
| D25235  | D25235 | 104221 | GEN-3   | Adrenergic receptor alpha 1c                                             | 1475 1039C>T | R347C |
| D25235  | D25235 | 104221 | GEN-3   | Adrenergic receptor alpha 1c                                             | 2048 1612C>T | 3     |
| D25418  | D25418 | 600022 | GEN-78  | Prostaglandin I2 (prostaglandin) receptor (IP)                           | 726 635G>A   | R212H |
| D25418  | D25418 | 600022 | GEN-78  | Prostaglandin I2 (prostaglandin) receptor (IP)                           | 1047 956C>G  | S319W |
| D25418  | D25418 | 600022 | GEN-78  | Prostaglandin I2 (prostaglandin) receptor (IP)                           | 1075 984A>C  | S     |
| D28538  | D28538 | 604102 | GEN-2DC | Metabotropic glutamate receptor type 5                                   | 531 381A>G   | S     |
| D32051  | D32051 | 138440 | GEN-4   | Glycinamide ribonucleotide transformylase                                | 25 (-47)G>A  | 5     |
| D32051  | D32051 | 138440 | GEN-4   | Glycinamide ribonucleotide transformylase                                | 1332 1261A>G | I421V |
| D32051  | D32051 | 138440 | GEN-4   | Glycinamide ribonucleotide transformylase                                | 1855 1784G>C | 3     |

|        |        |        |         |                                                                           |              |   |
|--------|--------|--------|---------|---------------------------------------------------------------------------|--------------|---|
| PTGIR  | D38128 | 600022 | GEN-4DH | transformylase<br>Human IP gene for prostacyclin receptor, exon 3         | 203 204C>G   | 3 |
| PTGIR  | D38128 | 600022 | GEN-4DH | Human IP gene for prostacyclin receptor, exon 3                           | 231 232C>A   | 3 |
| D38145 | D38145 | 601699 | GEN-4E3 | Human mRNA for prostacyclin synthase, complete cds                        | 1646 1619T>C | 3 |
| D45887 | D45887 | 114182 | GEN-BA  | Calmodulin 1 (phosphorylase kinase, delta)                                | 34 (-35)G>T  | 5 |
| D49394 | D49394 | 182139 | GEN-5   | Serotonin 5-HT receptors 5-HT3                                            | 1914 1695C>G | 3 |
| D50678 | D50678 | 602600 | GEN-30Y | Human mRNA for apolipoprotein E receptor 2, complete cds                  | 3378 3276G>A | 3 |
| D50678 | D50678 | 602600 | GEN-30Y | Human mRNA for apolipoprotein E receptor 2, complete cds                  | 3755 3653G>A | 3 |
| D50678 | D50678 | 602600 | GEN-30Y | Human mRNA for apolipoprotein E receptor 2, complete cds                  | 3949 3847G>C | 3 |
| D50678 | D50678 | 602600 | GEN-30Y | Human mRNA for apolipoprotein E receptor 2, complete cds                  | 4368 4266T>A | 3 |
| D50678 | D50678 | 602600 | GEN-30Y | Human mRNA for apolipoprotein E receptor 2, complete cds                  | 4455 4353G>A | 3 |
| D87673 | D87673 | 602438 | GEN-444 | Human mRNA for heat shock transcription factor 4, complete cds            | 274 270C>T   | S |
| D87673 | D87673 | 602438 | GEN-444 | Human mRNA for heat shock transcription factor 4, complete cds            | 1463 1459G>C | 3 |
| D87845 | D87845 | 602344 | GEN-44C | Human mRNA for platelet-activating factor acetylhydrolase 2, complete cds | 2299 2096G>A | 3 |
| D87845 | D87845 | 602344 | GEN-    | Human mRNA for platelet-                                                  | 2332 2129A>G | 3 |

|        | 44C           | activating factor                                       |                |
|--------|---------------|---------------------------------------------------------|----------------|
| D89052 | D89052 603717 | acetylhydrolase 2, complete cds                         | 5              |
| D89052 | D89052 603717 | Human mRNA for proton-ATPase-like protein, complete cds | 56 (-27)G>T    |
| D89052 | D89052 603717 | Human mRNA for proton-ATPase-like protein, complete cds | 3              |
| D89078 | D89078 601531 | complete cds                                            | 719 637G>A     |
| D89078 | D89078 601531 | P2Y7 purinoceptor                                       | 434 (-1284)A>T |
| D89078 | D89078 601531 | P2Y7 purinoceptor                                       | 889 (-829)G>C  |
| D89078 | D89078 601531 | P2Y7 purinoceptor                                       | 1156 (-562)G>C |
| D89078 | D89078 601531 | P2Y7 purinoceptor                                       | 2644 927T>C    |
| D89078 | D89078 601531 | P2Y7 purinoceptor                                       | 2920 1203A>G   |
| LRP1   | D90070 107770 | Human ATL-derived PMA-responsive (APR) peptide mRNA     | 3              |
| EDNRA  | D90348 131243 | Endothelin Receptor Type A                              | 1449 969C>T    |
| EDNRA  | D90348 131243 | Endothelin Receptor Type A                              | 1449 969C>T    |
| EDNRA  | D90348 131243 | Endothelin Receptor Type A                              | 1485 1005A>G   |
| EDNRA  | D90348 131243 | Endothelin Receptor Type A                              | 1485 1005A>G   |
| EDNRA  | D90348 131243 | Endothelin Receptor Type A                              | 1834 1354C>G   |
| EDNRA  | D90348 131243 | Endothelin Receptor Type A                              | 1834 1354C>G   |
| EDNRA  | D90348 131243 | Endothelin Receptor Type A                              | 2228 1748G>A   |
| EDNRA  | D90348 131243 | Endothelin Receptor Type A                              | 2376 1896G>A   |
| EDNRA  | D90348 131243 | Endothelin Receptor Type A                              | 2764 2284G>A   |
| EDNRA  | D90348 131243 | Endothelin Receptor Type A                              | 2764 2284G>A   |
| EDNRA  | D90348 131243 | Endothelin Receptor Type A                              | 2840 2360G>C   |
| EDNRA  | D90348 131243 | Endothelin Receptor Type A                              | 2935 2455G>A   |

|        |        |        |                |                                                          |              |       |
|--------|--------|--------|----------------|----------------------------------------------------------|--------------|-------|
| EDNRA  | D90348 | 131243 | 4DX<br>GEN-4DX | Endothelin Receptor Type A                               | 3294 2814A>G | 3     |
| J00123 | J00123 | 131330 | GEN-MK4        | Human enkephalin gene                                    | 81 81C>T     | S     |
| FGA    | J00127 | 134820 | GEN-T3         | Human fibrinogen alpha-chain mRNA, complete cds          | 560 530T>A   | I177N |
| FGA    | J00127 | 134820 | GEN-T3         | Human fibrinogen alpha-chain mRNA, complete cds          | 1138 1108G>T | A370S |
| J00129 | J00129 | 134830 | GEN-T4         | Human fibrinogen beta-chain mRNA, partial cds            | 543 543C>T   | S     |
| J00129 | J00129 | 134830 | GEN-T4         | Human fibrinogen beta-chain mRNA, partial cds            | 1101 1101C>T | S     |
| J00129 | J00129 | 134830 | GEN-T4         | Human fibrinogen beta-chain mRNA, partial cds            | 1409 1409G>A | R470K |
| J00137 | J00137 | 306900 | GEN-OX         | COAGULATION FACTOR IX                                    | 581 580A>G   | T194A |
| DHFR   | J00140 | 126060 | GEN-4E9        | Human dihydrofolate reductase gene                       | 721 679T>A   | 3     |
| DHFR   | J00140 | 126060 | GEN-4E9        | Human dihydrofolate reductase gene                       | 721 679T>A   | 3     |
| DHFR   | J00140 | 126060 | GEN-4E9        | Human dihydrofolate reductase gene                       | 829 787C>T   | 3     |
| J02611 | J02611 | 107740 | GEN-6O         | Human apolipoprotein D mRNA, complete cds                | 676 615T>G   | 3     |
| J02611 | J02611 | 107740 | GEN-6O         | Human apolipoprotein D mRNA, complete cds                | 683 622T>G   | 3     |
| J02611 | J02611 | 107740 | GEN-6O         | Human apolipoprotein D mRNA, complete cds                | 701 640C>G   | 3     |
| J02611 | J02611 | 107740 | GEN-6O         | Human apolipoprotein D mRNA, complete cds                | 745 684A>G   | 3     |
| CBG    | J02943 | 122500 | GEN-Y2         | Human corticosteroid binding globulin mRNA, complete cds | 106 71A>T    | D24V  |
| CBG    | J02943 | 122500 | GEN-Y2         | Human corticosteroid binding globulin mRNA, complete cds | 971 936T>C   | S     |
| CBG    | J02943 | 122500 | GEN-Y2         | Human corticosteroid binding globulin mRNA, complete cds | 1229 1194G>A | S     |
| J03143 | J03143 | 107470 | GEN-ZK         | Human interferon-gamma                                   | 1098 1050T>G | S     |

|        |        |        |         |                                               |              |       |
|--------|--------|--------|---------|-----------------------------------------------|--------------|-------|
| J03242 | J03242 | 147470 | GEN-PJ  | receptor mRNA, complete cds                   | 932 380G>A   | R127H |
| J03242 | J03242 | 147470 | GEN-PJ  | Insulin-like growth factor 2                  | 1063 511G>A  | A171T |
| J03242 | J03242 | 147470 | GEN-PJ  | Insulin-like growth factor 2                  | 1190 638C>G  | 3     |
| J03242 | J03242 | 147470 | GEN-PJ  | Insulin-like growth factor 2                  | 1201 649C>T  | 3     |
| J03258 | J03258 | 601769 | GEN-2J  | Vitamin D (1,25-dihydroxyvitamin D3) receptor | 172 57C>T    | S     |
| J03258 | J03258 | 601769 | GEN-2J  | Vitamin D (1,25-dihydroxyvitamin D3) receptor | 559 444C>T   | S     |
| J03258 | J03258 | 601769 | GEN-2J  | Vitamin D (1,25-dihydroxyvitamin D3) receptor | 1704 1589C>A | 3     |
| J03258 | J03258 | 601769 | GEN-2J  | Vitamin D (1,25-dihydroxyvitamin D3) receptor | 1833 1718C>G | 3     |
| J03258 | J03258 | 601769 | GEN-2J  | Vitamin D (1,25-dihydroxyvitamin D3) receptor | 1959 1844A>C | 3     |
| J03258 | J03258 | 601769 | GEN-2J  | Vitamin D (1,25-dihydroxyvitamin D3) receptor | 3301 3186C>A | 3     |
| J03258 | J03258 | 601769 | GEN-2J  | Vitamin D (1,25-dihydroxyvitamin D3) receptor | 3991 3876A>G | 3     |
| J03258 | J03258 | 601769 | GEN-2J  | Vitamin D (1,25-dihydroxyvitamin D3) receptor | 4187 4072G>A | 3     |
| J03258 | J03258 | 601769 | GEN-2J  | Vitamin D (1,25-dihydroxyvitamin D3) receptor | 4187 4072G>A | 3     |
| CHGA   | J03483 | 118910 | GEN-11E | Human chromogranin A mRNA, complete cds       | 583 501T>G   | N167K |
| CHGA   | J03483 | 118910 | GEN-11E | Human chromogranin A mRNA, complete cds       | 1405 1323A>G | S     |
| CHGA   | J03483 | 118910 | GEN-11E | Human chromogranin A mRNA, complete cds       | 1543 1461C>T | 3     |



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|--------|--------|--------|--------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------|-------|
| J03490 | J03490 | 246900 | GEN-C5 | Dihydrolipoamide<br>dehydrogenase (E3<br>component of pyruvate<br>dehydrogenase complex,<br>2-oxo-glutarate complex,<br>branched chain keto acid<br>dehydrogenase complex) | 1569 1493A>C | N498T |
| J03490 | J03490 | 246900 | GEN-C5 | Dihydrolipoamide<br>dehydrogenase (E3<br>component of pyruvate<br>dehydrogenase complex,<br>2-oxo-glutarate complex,<br>branched chain keto acid<br>dehydrogenase complex) | 1624 1548T>A | 3     |
| J03490 | J03490 | 246900 | GEN-C5 | Dihydrolipoamide<br>dehydrogenase (E3<br>component of pyruvate<br>dehydrogenase complex,<br>2-oxo-glutarate complex,<br>branched chain keto acid<br>dehydrogenase complex) | 1813 1737A>G | 3     |
| J03490 | J03490 | 246900 | GEN-C5 | Dihydrolipoamide<br>dehydrogenase (E3<br>component of pyruvate<br>dehydrogenase complex,<br>2-oxo-glutarate complex,<br>branched chain keto acid<br>dehydrogenase complex) | 2096 2020T>C | 3     |
| J03778 | J03778 | 157140 | GEN-C7 | MICROTUBULE-<br>ASSOCIATED PROTEIN<br>TAU                                                                                                                                  | 391 354G>A   | S     |
| J03853 | J03853 | 104250 | GEN-A  | Adrenergic receptor alpha<br>2c                                                                                                                                            | 1202 1164C>T | S     |
| J03853 | J03853 | 104250 | GEN-A  | Adrenergic receptor alpha<br>2c                                                                                                                                            | 1237 1199T>G | I400S |
| J03853 | J03853 | 104250 | GEN-A  | Adrenergic receptor alpha<br>2c                                                                                                                                            | 1372 1334C>G | P445R |
| J03853 | J03853 | 104250 | GEN-A  | Adrenergic receptor alpha<br>2c                                                                                                                                            | 1379 1341C>T | S     |
| J04031 | J04031 | 172460 | GEN-CB | Methenyltetrahydrofolate<br>cyclohydrolase                                                                                                                                 | 454 401G>A   | R134K |

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|--------|--------|--------|-------------|--------------------------------------------|---------------------------------------|---------------------------------|
| J04031 | J04031 | 172460 | GEN-CB      | Methenyltetrahydrofolate<br>cyclohydrolase | 969 916C>G                            | Q306E                           |
| J04031 | J04031 | 172460 | GEN-CB      | Methenyltetrahydrofolate<br>cyclohydrolase | 1614 1561T>C                          | S                               |
| J04031 | J04031 | 172460 | GEN-CB      | Methenyltetrahydrofolate<br>cyclohydrolase | 2011 1958G>A                          | R653Q                           |
| J04031 | J04031 | 172460 | GEN-CB      | Methenyltetrahydrofolate<br>cyclohydrolase | 2335 2282C>T                          | T761M                           |
| J04046 | J04046 | 114183 | GEN-<br>13N | Human calmodulin mRNA,<br>complete cds     | 791 688C>T                            | 3                               |
| J04046 | J04046 | 114183 | GEN-<br>13N | Human calmodulin mRNA,<br>complete cds     | 881 778T>C                            | 3                               |
| J04046 | J04046 | 114183 | GEN-<br>13N | Human calmodulin mRNA,<br>complete cds     | 1927 1824T>C                          | 3                               |
| J04144 | J04144 | 106180 | GEN-2L      | Angiotensin-converting<br>enzyme (ACE)     | 803 781G>T                            | A261S                           |
| J04144 | J04144 | 106180 | GEN-2L      | Angiotensin-converting<br>enzyme (ACE)     | 1042 1020C>T                          | S                               |
| J04144 | J04144 | 106180 | GEN-2L      | Angiotensin-converting<br>enzyme (ACE)     | 1535 1513-<br>1515CCT>CC<br>T         | S                               |
| J04144 | J04144 | 106180 | GEN-2L      | Angiotensin-converting<br>enzyme (ACE)     | 1535 1513-<br>1515delCCT<br>6-505del] | [P505V;50<br>6-505del]<br>D592G |
| J04144 | J04144 | 106180 | GEN-2L      | Angiotensin-converting<br>enzyme (ACE)     | 1797 1775A>G                          | S                               |
| J04144 | J04144 | 106180 | GEN-2L      | Angiotensin-converting<br>enzyme (ACE)     | 2215 2193G>A                          | S                               |
| J04144 | J04144 | 106180 | GEN-2L      | Angiotensin-converting<br>enzyme (ACE)     | 2350 2328A>G                          | S                               |
| J04144 | J04144 | 106180 | GEN-2L      | Angiotensin-converting<br>enzyme (ACE)     | 2505 2483T>C                          | M828T                           |
| J04144 | J04144 | 106180 | GEN-2L      | Angiotensin-converting<br>enzyme (ACE)     | 3409 3387T>C                          | S                               |
| J04144 | J04144 | 106180 | GEN-2L      | Angiotensin-converting<br>enzyme (ACE)     | 3409 3387T>C                          | S                               |
| J05158 | J05158 | 603104 | GEN-173     | Human carboxypeptidase<br>N mRNA, 3 end    | 2314 2314C>T                          | 3                               |
| J05158 | J05158 | 603104 | GEN-173     | Human carboxypeptidase<br>N mRNA, 3 end    | 2316 2316G>T                          | 3                               |
| J05158 | J05158 | 603104 | GEN-173     | Human carboxypeptidase<br>N mRNA, 3 end    | 2332 2332G>T                          | 3                               |

|        |        |        |         |                                                             |                |        |
|--------|--------|--------|---------|-------------------------------------------------------------|----------------|--------|
| J05158 | J05158 | 603104 | GEN-173 | Human carboxypeptidase<br>N mRNA, 3 end                     | 2541 2541G>A   | 3      |
| J05158 | J05158 | 603104 | GEN-173 | Human carboxypeptidase<br>N mRNA, 3 end                     | 2651 2651C>T   | 3      |
| J05176 | J05176 | 107280 | GEN-PT  | Human alpha-1-<br>antichymotrypsin mRNA, 3<br>end           | 240 240A>G     | S      |
| J05176 | J05176 | 107280 | GEN-PT  | Human alpha-1-<br>antichymotrypsin mRNA, 3<br>end           | 327 327C>T     | S      |
| J05176 | J05176 | 107280 | GEN-PT  | Human alpha-1-<br>antichymotrypsin mRNA, 3<br>end           | 554 554T>C     | V185A  |
| J05200 | J05200 | 180901 | GEN-17B | Human ryanodine receptor<br>mRNA, complete cds              | 14981 14876G>T | G4959V |
| J05594 | J05594 | 601688 | GEN-E   | Prostaglandin 15-OH<br>dehydrogenase (PGDH)                 | 173 156A>G     | S      |
| J05594 | J05594 | 601688 | GEN-E   | Prostaglandin 15-OH<br>dehydrogenase (PGDH)                 | 913 896C>G     | 3      |
| J05594 | J05594 | 601688 | GEN-E   | Prostaglandin 15-OH<br>dehydrogenase (PGDH)                 | 950 933G>A     | 3      |
| J05594 | J05594 | 601688 | GEN-E   | Prostaglandin 15-OH<br>dehydrogenase (PGDH)                 | 1448 1431G>A   | 3      |
| J05594 | J05594 | 601688 | GEN-E   | Prostaglandin 15-OH<br>dehydrogenase (PGDH)                 | 1972 1955T>C   | 3      |
| J05594 | J05594 | 601688 | GEN-E   | Prostaglandin 15-OH<br>dehydrogenase (PGDH)                 | 1972 1955T>C   | 3      |
| K00396 | K00396 | 107741 | GEN-P0  | Human apolipoprotein E<br>(epsilon 2 and 3 alleles)<br>mRNA | 121 61G>A      | E21K   |
| K00396 | K00396 | 107741 | GEN-P0  | Human apolipoprotein E<br>(epsilon 2 and 3 alleles)<br>mRNA | 151 91G>A      | E31K   |
| K00396 | K00396 | 107741 | GEN-P0  | Human apolipoprotein E<br>(epsilon 2 and 3 alleles)<br>mRNA | 197 137T>C     | L46P   |
| K00396 | K00396 | 107741 | GEN-P0  | Human apolipoprotein E<br>(epsilon 2 and 3 alleles)<br>mRNA | 204 144delG    | F      |
| K00396 | K00396 | 107741 | GEN-P0  | Human apolipoprotein E<br>(epsilon 2 and 3 alleles)<br>mRNA | 238 178A>G     | T60A   |

|        |        |        |        |                                                             |            |       |
|--------|--------|--------|--------|-------------------------------------------------------------|------------|-------|
| K00396 | K00396 | 107741 | GEN-P0 | Human apolipoprotein E<br>(epsilon 2 and 3 alleles)<br>mRNA | 365 305C>G | P102R |
| K00396 | K00396 | 107741 | GEN-P0 | Human apolipoprotein E<br>(epsilon 2 and 3 alleles)<br>mRNA | 409 349G>A | A117T |
| K00396 | K00396 | 107741 | GEN-P0 | Human apolipoprotein E<br>(epsilon 2 and 3 alleles)<br>mRNA | 448 388T>C | C130R |
| K00396 | K00396 | 107741 | GEN-P0 | Human apolipoprotein E<br>(epsilon 2 and 3 alleles)<br>mRNA | 494 434G>A | G145D |
| K00396 | K00396 | 107741 | GEN-P0 | Human apolipoprotein E<br>(epsilon 2 and 3 alleles)<br>mRNA | 515 455G>A | R152Q |
| K00396 | K00396 | 107741 | GEN-P0 | Human apolipoprotein E<br>(epsilon 2 and 3 alleles)<br>mRNA | 520 460C>A | R154S |
| K00396 | K00396 | 107741 | GEN-P0 | Human apolipoprotein E<br>(epsilon 2 and 3 alleles)<br>mRNA | 538 478C>T | R160C |
| K00396 | K00396 | 107741 | GEN-P0 | Human apolipoprotein E<br>(epsilon 2 and 3 alleles)<br>mRNA | 547 487C>T | R163C |
| K00396 | K00396 | 107741 | GEN-P0 | Human apolipoprotein E<br>(epsilon 2 and 3 alleles)<br>mRNA | 548 488G>A | R163H |
| K00396 | K00396 | 107741 | GEN-P0 | Human apolipoprotein E<br>(epsilon 2 and 3 alleles)<br>mRNA | 550 490A>G | K164E |
| K00396 | K00396 | 107741 | GEN-P0 | Human apolipoprotein E<br>(epsilon 2 and 3 alleles)<br>mRNA | 586 526C>T | R176C |
| K00396 | K00396 | 107741 | GEN-P0 | Human apolipoprotein E<br>(epsilon 2 and 3 alleles)<br>mRNA | 586 526C>T | R176C |
| K00396 | K00396 | 107741 | GEN-P0 | Human apolipoprotein E<br>(epsilon 2 and 3 alleles)<br>mRNA | 743 683G>A | F     |
| K00396 | K00396 | 107741 | GEN-P0 | Human apolipoprotein E<br>(epsilon 2 and 3 alleles)<br>mRNA | 785 725G>A | R242Q |

|        |        |        |        |                                                                               |              |       |
|--------|--------|--------|--------|-------------------------------------------------------------------------------|--------------|-------|
| K00396 | K00396 | 107741 | GEN-P0 | (epsilon 2 and 3 alleles)<br>mRNA                                             | 796 736C>T   | R246C |
| K00396 | K00396 | 107741 | GEN-P0 | Human apolipoprotein E<br>(epsilon 2 and 3 alleles)<br>mRNA                   | 821 761T>A   | V254E |
| K00396 | K00396 | 107741 | GEN-P0 | Human apolipoprotein E<br>(epsilon 2 and 3 alleles)<br>mRNA                   | 865 805C>G   | R269G |
| K00396 | K00396 | 107741 | GEN-P0 | Human apolipoprotein E<br>(epsilon 2 and 3 alleles)<br>mRNA                   | 935 875G>A   | R292H |
| K00396 | K00396 | 107741 | GEN-P0 | Human apolipoprotein E<br>(epsilon 2 and 3 alleles)<br>mRNA                   | 1000 940A>C  | S314R |
| K00557 | K00557 | 602529 | GEN-TY | human alpha-tubulin<br>mRNA, 3 end                                            | 126 126G>C   | S     |
| K01911 | K01911 | 162640 | GEN-2O | Neuropeptide Y                                                                | 236 150G>A   | S     |
| K01911 | K01911 | 162640 | GEN-2O | Neuropeptide Y                                                                | 290 204C>T   | S     |
| AGT    | K02215 | 106150 | GEN-WK | Human angiotensinogen<br>mRNA, complete CDS                                   | 659 620C>T   | T207M |
| AGT    | K02215 | 106150 | GEN-WK | Human angiotensinogen<br>mRNA, complete CDS                                   | 842 803T>C   | M268T |
| AGT    | K02215 | 106150 | GEN-WK | Human angiotensinogen<br>mRNA, complete CDS                                   | 1155 1116G>A | S     |
| AGT    | K02215 | 106150 | GEN-WK | Human angiotensinogen<br>mRNA, complete CDS                                   | 1476 1437C>A | S     |
| AGT    | K02215 | 106150 | GEN-WK | Human angiotensinogen<br>mRNA, complete CDS                                   | 1821 1782G>A | 3     |
| AGT    | K02215 | 106150 | GEN-WK | Human angiotensinogen<br>mRNA, complete CDS                                   | 2053 2014A>C | 3     |
| KNG    | K02566 | 228960 | GEN-X2 | Human alpha-2-thiol<br>proteinase inhibitor mRNA,<br>complete coding sequence | 1248 1199C>A | T400K |
| K02770 | K02770 | 147720 | GEN-5M | Interleukin 1, beta                                                           | 19 (-68)A>C  | 5     |
| K02770 | K02770 | 147720 | GEN-5M | Interleukin 1, beta                                                           | 26 (-61)A>C  | 5     |
| K02770 | K02770 | 147720 | GEN-5M | Interleukin 1, beta                                                           | 48 (-39)C>T  | 5     |
| K02770 | K02770 | 147720 | GEN-5M | Interleukin 1, beta                                                           | 114 28G>A    | E10K  |

|        |        |        |         |                                                                                       |                                                        |       |
|--------|--------|--------|---------|---------------------------------------------------------------------------------------|--------------------------------------------------------|-------|
| K02770 | K02770 | 147720 | GEN-5M  | Interleukin 1, beta                                                                   | 119 33G>A                                              | M11I  |
| L03558 | L03558 | 601145 | GEN-11O | Homo sapiens cystatin B mRNA, complete cds                                            | 485 390A>G                                             | 3     |
| L05597 | L05597 | None   | GEN-4EV | Serotonin 5-HT receptors 5-HT1F                                                       | 824 600T>C                                             | S     |
| L05597 | L05597 | None   | GEN-4EV | Serotonin 5-HT receptors 5-HT1F                                                       | 1010 786^787insA [H262Q;26 ATAAAATTC 2^263insl AT KFI] | 5     |
| EDNRB  | L06623 | 131244 | GEN-19S | Endothelin Receptor Type B                                                            | 88 (-146)A>G                                           | 5     |
| EDNRB  | L06623 | 131244 | GEN-19S | Endothelin Receptor Type B                                                            | 332 99C>T                                              | S     |
| EDNRB  | L06623 | 131244 | GEN-19S | Endothelin Receptor Type B                                                            | 1064 831G>A                                            | S     |
| EDNRB  | L06623 | 131244 | GEN-19S | Endothelin Receptor Type B                                                            | 1064 831G>A                                            | S     |
| TGFBR3 | L07594 | 600742 | GEN-1EA | Human transforming growth factor-beta type III receptor (TGF-beta) mRNA, complete cds | 3966 3618G>C                                           | 3     |
| L07861 | L07861 | 176977 | GEN-D0  | Protein kinase C, delta                                                               | 445 387G>A                                             | S     |
| L07861 | L07861 | 176977 | GEN-D0  | Protein kinase C, delta                                                               | 1835 1777G>A                                           | V593M |
| GNRHR  | L07949 | 138850 | GEN-1F1 | Gonadotropin releasing hormone agonist                                                | 1371 1347C>A                                           | 3     |
| CCKBR  | L08112 | 118445 | GEN-1FL | Cholecystokinin (CCKb)                                                                | 456 456G>A                                             | S     |
| L08485 | L08485 | 137142 | GEN-G   | Gamma-aminobutyric acid (GABA) A receptor, alpha 5                                    | 1646 1341G>T                                           | S     |
| L08485 | L08485 | 137142 | GEN-G   | Gamma-aminobutyric acid (GABA) A receptor, alpha 5                                    | 2113 1808C>T                                           | 3     |
| INPP1  | L08488 | 147263 | GEN-1FY | Human inositol polyphosphate 1-phosphatase mRNA, complete cds                         | 185 (-142)T>G                                          | 5     |
| INPP1  | L08488 | 147263 | GEN-1FY | Human inositol polyphosphate 1-phosphatase mRNA, complete cds                         | 479 153T>G                                             | S     |
| INPP1  | L08488 | 147263 | GEN-    | Human inositol polyphosphate 1-phosphatase mRNA, complete cds                         | 674 348A>G                                             | S     |

|        |        |        |         |                                                               |            |      |
|--------|--------|--------|---------|---------------------------------------------------------------|------------|------|
| INPP1  | L08488 | 147263 | GEN-1FY | polyphosphate 1-phosphatase mRNA, complete cds                | 806 480G>A | S    |
| MIF    | L10612 | 153620 | GEN-1J8 | Human inositol polyphosphate 1-phosphatase mRNA, complete cds | 170 96C>G  | S    |
| MIF    | L10612 | 153620 | GEN-1J8 | Human glycosylation-inhibiting factor mRNA, complete cds      | 221 147C>G | S    |
| MIF    | L10612 | 153620 | GEN-1J8 | Human glycosylation-inhibiting factor mRNA, complete cds      | 227 153C>G | S    |
| MIF    | L10612 | 153620 | GEN-1J8 | Human glycosylation-inhibiting factor mRNA, complete cds      | 239 165G>A | S    |
| MIF    | L10612 | 153620 | GEN-1J8 | Human glycosylation-inhibiting factor mRNA, complete cds      | 329 255C>A | S    |
| MIF    | L10612 | 153620 | GEN-1J8 | Human glycosylation-inhibiting factor mRNA, complete cds      | 445 371C>T | 3    |
| L10819 | L10819 | 171150 | GEN-LVD | Homo sapiens aryl sulfotransferase mRNA, complete cds         | 191 153C>T | S    |
| L10819 | L10819 | 171150 | GEN-LVD | Homo sapiens aryl sulfotransferase mRNA, complete cds         | 200 162G>A | S    |
| L10819 | L10819 | 171150 | GEN-LVD | Homo sapiens aryl sulfotransferase mRNA, complete cds         | 230 192T>C | S    |
| L10819 | L10819 | 171150 | GEN-LVD | Homo sapiens aryl sulfotransferase mRNA, complete cds         | 242 204G>A | S    |
| L10819 | L10819 | 171150 | GEN-LVD | Homo sapiens aryl sulfotransferase mRNA, complete cds         | 295 257C>T | A86V |
| L10819 | L10819 | 171150 | GEN-LVD | Homo sapiens aryl sulfotransferase mRNA, complete cds         | 330 292G>A | D98N |

|        |        |        |        |         |                                                                                       |              |       |
|--------|--------|--------|--------|---------|---------------------------------------------------------------------------------------|--------------|-------|
| L10819 | L10819 | L10819 | 171150 | GEN-LVD | sulfotransferase mRNA,<br>complete cds<br>Homo sapiens aryl<br>sulfotransferase mRNA, |              | S     |
| L10819 | L10819 | L10819 | 171150 | GEN-LVD | complete cds<br>Homo sapiens aryl<br>sulfotransferase mRNA,                           | 338 300G>A   | S     |
| L10819 | L10819 | L10819 | 171150 | GEN-LVD | complete cds<br>Homo sapiens aryl<br>sulfotransferase mRNA,                           | 638 600C>G   | S     |
| L10819 | L10819 | L10819 | 171150 | GEN-LVD | complete cds<br>Homo sapiens aryl<br>sulfotransferase mRNA,                           | 676 638A>G   | H213R |
| L10819 | L10819 | L10819 | 171150 | GEN-LVD | complete cds<br>Homo sapiens aryl<br>sulfotransferase mRNA,                           | 940 902G>A   | 3     |
| L10819 | L10819 | L10819 | 171150 | GEN-LVD | complete cds<br>Homo sapiens aryl<br>sulfotransferase mRNA,                           | 1011 973T>C  | 3     |
| L11005 | L11005 | L11005 | 602841 | GEN-1JU | Human aldehyde oxidase<br>(hAOX) mRNA, complete<br>cds                                | 4284 4154C>A | 3     |
| L11005 | L11005 | L11005 | 602841 | GEN-1JU | Human aldehyde oxidase<br>(hAOX) mRNA, complete<br>cds                                | 4447 4317G>C | 3     |
| L11005 | L11005 | L11005 | 602841 | GEN-1JU | Human aldehyde oxidase<br>(hAOX) mRNA, complete<br>cds                                | 4525 4395T>G | 3     |
| L11005 | L11005 | L11005 | 602841 | GEN-1JU | Human aldehyde oxidase<br>(hAOX) mRNA, complete<br>cds                                | 4675 4545G>A | 3     |
| L11667 | L11667 | L11667 | 601753 | GEN-H   | Cyclophilin D 40kDa                                                                   | 1003 904C>A  | L302I |
| L11667 | L11667 | L11667 | 601753 | GEN-H   | Cyclophilin D 40kDa                                                                   | 1283 1184A>G | 3     |
| L11667 | L11667 | L11667 | 601753 | GEN-H   | Cyclophilin D 40kDa                                                                   | 1479 1380T>A | 3     |
| L11667 | L11667 | L11667 | 601753 | GEN-H   | Cyclophilin D 40kDa                                                                   | 1519 1420T>C | 3     |
| L11931 | L11931 | L11931 | 182144 | GEN-4DT | Human cytosolic serine<br>hydroxymethyltransferase<br>(SHMT) mRNA, complete<br>cds    | 1444 1420C>T | L474F |
| L11931 | L11931 | L11931 | 182144 | GEN-4DT | Human cytosolic serine<br>hydroxymethyltransferase<br>(SHMT) mRNA, complete<br>cds    | 1541 1517C>T | 3     |



|        |        |        |         |                                                                                      |              |       |
|--------|--------|--------|---------|--------------------------------------------------------------------------------------|--------------|-------|
| L12052 | L12052 | 171885 | GEN-1LK | Human cAMP phosphodiesterase mRNA, 3 end                                             | 1707 1707G>A | 3     |
| L13266 | L13266 | 138249 | GEN-J   | Glutamate Aspartate receptor NMDA 1                                                  | 1618 525G>C  | S     |
| L13266 | L13266 | 138249 | GEN-J   | Glutamate Aspartate receptor NMDA 1                                                  | 1792 699C>A  | S     |
| L13266 | L13266 | 138249 | GEN-J   | Glutamate Aspartate receptor NMDA 1                                                  | 1948 855G>A  | S     |
| L13266 | L13266 | 138249 | GEN-J   | Glutamate Aspartate receptor NMDA 1                                                  | 2713 1620T>G | I540M |
| L13266 | L13266 | 138249 | GEN-J   | Glutamate Aspartate receptor NMDA 1                                                  | 3137 2044G>T | A682S |
| L13266 | L13266 | 138249 | GEN-J   | Glutamate Aspartate receptor NMDA 1                                                  | 3241 2148G>A | S     |
| MDCR   | L13385 | 601545 | GEN-1O6 | Glutamate Aspartate receptor NMDA 1                                                  | 1467 1250C>T | 3     |
| MDCR   | L13385 | 601545 | GEN-1O6 | Homo sapiens(clone 71) Miller-Dieker lissencephaly protein (LIS1) mRNA, complete cds | 1868 1651C>T | 3     |
| MDCR   | L13385 | 601545 | GEN-1O6 | Homo sapiens(clone 71) Miller-Dieker lissencephaly protein (LIS1) mRNA, complete cds | 1917 1700C>T | 3     |
| MDCR   | L13385 | 601545 | GEN-1O6 | Homo sapiens(clone 71) Miller-Dieker lissencephaly protein (LIS1) mRNA, complete cds | 2962 2745G>T | 3     |
| MDCR   | L13385 | 601545 | GEN-1O6 | Homo sapiens(clone 71) Miller-Dieker lissencephaly protein (LIS1) mRNA, complete cds | 4589 4372G>A | 3     |
| L13436 | L13436 | 108961 | GEN-2Q  | guanylate cyclase                                                                    | 2222 2223C>T | 3     |
| L13436 | L13436 | 108961 | GEN-2Q  | guanylate cyclase                                                                    | 2444 2445C>T | 3     |
| L13977 | L13977 | 176785 | GEN-1PX | Human prollycarboxypeptidase mRNA, complete cds                                      | 2009 1980T>C | 3     |
| CAMK4  | L17000 | 114080 | GEN-    | Homo sapiens                                                                         | 1381 1340C>T | A447V |

| 1ZR     | calcium/calmodulin-dependent protein kinase mRNA, complete cds |        |        |              |       |
|---------|----------------------------------------------------------------|--------|--------|--------------|-------|
| GEN-1ZQ | L17075                                                         | L17075 | 601284 | 838 747G>A   | S     |
| GEN-21N | PRKCI                                                          | L18964 | 300094 | 573 309T>G   | S     |
| GEN-22D | L19760                                                         | L19760 | 600322 | 259 171C>G   | S     |
| GEN-22D | L19760                                                         | L19760 | 600322 | 418 330T>C   | S     |
| GEN-22D | L19760                                                         | L19760 | 600322 | 629 541A>T   | I181F |
| GEN-LVE | L19956                                                         | L19956 | 600641 | 243 105A>G   | S     |
| GEN-LVE | L19956                                                         | L19956 | 600641 | 284 146C>T   | S49F  |
| GEN-23G | HD                                                             | L20431 | 143100 | 1536 1535T>G | I512S |
| GEN-23G | HD                                                             | L20431 | 143100 | 2112 2111C>G | 3     |
| GEN-23G | HD                                                             | L20431 | 143100 | 3788 3787G>A | 3     |
| GEN-23G | HD                                                             | L20431 | 143100 | 4912 4911G>A | 3     |
| GEN-23G | HD                                                             | L20431 | 143100 | 5454 5453C>T | 3     |
| GEN-M   | L20463                                                         | L20463 | 600445 | 1671 1380A>G | 3     |

|        |        |        |         |                                                                      |               |   |
|--------|--------|--------|---------|----------------------------------------------------------------------|---------------|---|
| VLDLR  | L20470 | 192977 | GEN-23D | Human very low density lipoprotein receptor mRNA, complete cds       | 336 (-56)C>T  | 5 |
| VLDLR  | L20470 | 192977 | GEN-23D | Human very low density lipoprotein receptor mRNA, complete cds       | 3566 3175T>C  | 3 |
| SOAT   | L21934 | 102642 | GEN-25C | Human acyl coenzyme A:cholesterol acyltransferase mRNA, complete cds | 676 (-721)T>G | 5 |
| SOAT   | L21934 | 102642 | GEN-25C | Human acyl coenzyme A:cholesterol acyltransferase mRNA, complete cds | 814 (-583)C>T | 5 |
| SOAT   | L21934 | 102642 | GEN-25C | Human acyl coenzyme A:cholesterol acyltransferase mRNA, complete cds | 1993 597C>T   | S |
| SOAT   | L21934 | 102642 | GEN-25C | Human acyl coenzyme A:cholesterol acyltransferase mRNA, complete cds | 2365 969C>T   | S |
| SOAT   | L21934 | 102642 | GEN-25C | Human acyl coenzyme A:cholesterol acyltransferase mRNA, complete cds | 2821 1425G>C  | S |
| SOAT   | L21934 | 102642 | GEN-25C | Human acyl coenzyme A:cholesterol acyltransferase mRNA, complete cds | 3537 2141T>C  | 3 |
| L22214 | L22214 | 102775 | GEN-2S  | Adenosine A1 receptor (ADORA1)                                       | 557 147G>C    | S |
| L22214 | L22214 | 102775 | GEN-2S  | Adenosine A1 receptor (ADORA1)                                       | 2622 2212G>A  | 3 |
| SLC6A3 | L24178 | 126455 | GEN-283 | Homo sapiens dopamine transporter mRNA, complete cds                 | 1917 1898C>T  | 3 |
| L24470 | L24470 | 600563 | GEN-O   | PROSTAGLANDIN F RECEPTOR                                             | 1422 1185T>C  | 3 |
| L24470 | L24470 | 600563 | GEN-O   | PROSTAGLANDIN F RECEPTOR                                             | 1490 1253C>T  | 3 |

|        |        |        |             |                                                          |               |       |
|--------|--------|--------|-------------|----------------------------------------------------------|---------------|-------|
| L24470 | L24470 | 600563 | GEN-O       | PROSTAGLANDIN F<br>RECEPTOR                              | 1517 1280A>G  | 3     |
| L24470 | L24470 | 600563 | GEN-O       | PROSTAGLANDIN F<br>RECEPTOR                              | 2244 2007A>G  | 3     |
| L24470 | L24470 | 600563 | GEN-O       | PROSTAGLANDIN F<br>RECEPTOR                              | 2299 2062A>G  | 3     |
| OPRM1  | L25119 | 600018 | GEN-<br>4EP | Human Mu opiate receptor<br>(MOR1) mRNA, complete<br>cds | 41 (-172)G>T  | 5     |
| OPRM1  | L25119 | 600018 | GEN-<br>4EP | Human Mu opiate receptor<br>(MOR1) mRNA, complete<br>cds | 102 (-111)C>T | 5     |
| OPRM1  | L25119 | 600018 | GEN-<br>4EP | Human Mu opiate receptor<br>(MOR1) mRNA, complete<br>cds | 229 17C>T     | A6V   |
| OPRM1  | L25119 | 600018 | GEN-<br>4EP | Human Mu opiate receptor<br>(MOR1) mRNA, complete<br>cds | 229 17C>T     | A6V   |
| OPRM1  | L25119 | 600018 | GEN-<br>4EP | Human Mu opiate receptor<br>(MOR1) mRNA, complete<br>cds | 236 24G>A     | S     |
| OPRM1  | L25119 | 600018 | GEN-<br>4EP | Human Mu opiate receptor<br>(MOR1) mRNA, complete<br>cds | 330 118A>G    | N40D  |
| OPRM1  | L25119 | 600018 | GEN-<br>4EP | Human Mu opiate receptor<br>(MOR1) mRNA, complete<br>cds | 330 118A>G    | N40D  |
| OPRM1  | L25119 | 600018 | GEN-<br>4EP | Human Mu opiate receptor<br>(MOR1) mRNA, complete<br>cds | 991 779G>A    | R260H |
| OPRM1  | L25119 | 600018 | GEN-<br>4EP | Human Mu opiate receptor<br>(MOR1) mRNA, complete<br>cds | 1005 793C>T   | R265C |
| OPRM1  | L25119 | 600018 | GEN-<br>4EP | Human Mu opiate receptor<br>(MOR1) mRNA, complete<br>cds | 1154 942G>A   | S     |
| OPRM1  | L25119 | 600018 | GEN-<br>4EP | Human Mu opiate receptor<br>(MOR1) mRNA, complete<br>cds | 1154 942G>A   | S     |
| L26232 | L26232 | 172425 | GEN-<br>2AK | Human phospholipid<br>transfer protein mRNA,<br>cds      | 906 819C>T    | S     |

|        |        |        |         |                                                                |              |        |
|--------|--------|--------|---------|----------------------------------------------------------------|--------------|--------|
| L26232 | L26232 | 172425 | GEN-2AK | complete cds<br>Human phospholipid transfer protein mRNA,      | 1547 1460C>A | T487K  |
| PTGER2 | L28175 | 601586 | GEN-7C  | complete cds<br>Prostaglandin E receptor 2 (subtype EP2), 53kD | 547 159C>T   | S      |
| PTGER2 | L28175 | 601586 | GEN-7C  | Prostaglandin E receptor 2 (subtype EP2), 53kD                 | 611 223G>A   | V75M   |
| PTGER2 | L28175 | 601586 | GEN-7C  | Prostaglandin E receptor 2 (subtype EP2), 53kD                 | 1725 1337A>G | Q446R  |
| L31773 | L31773 | 104220 | GEN-4DD | Adrenergic receptor alpha 1b                                   | 171 171C>T   | S      |
| L31773 | L31773 | 104220 | GEN-4DD | Adrenergic receptor alpha 1b                                   | 534 534C>T   | S      |
| L31773 | L31773 | 104220 | GEN-4DD | Adrenergic receptor alpha 1b                                   | 549 549G>A   | S      |
| L33798 | L33798 | 114208 | GEN-Q   | Ca Channel alpha1s L-Type                                      | 5667 5442C>G | S      |
| L33798 | L33798 | 114208 | GEN-Q   | Ca Channel alpha1s L-Type                                      | 5669 5444G>C | G1815A |
| L33798 | L33798 | 114208 | GEN-Q   | Ca Channel alpha1s L-Type                                      | 5745 5520C>G | D1840E |
| L33798 | L33798 | 114208 | GEN-Q   | Ca Channel alpha1s L-Type                                      | 5941 5716C>A | 3      |
| L33798 | L33798 | 114208 | GEN-Q   | Ca Channel alpha1s L-Type                                      | 5971 5746C>A | 3      |
| L33798 | L33798 | 114208 | GEN-Q   | Ca Channel alpha1s L-Type                                      | 5985 5760G>A | 3      |
| L36151 | L36151 | 600286 | GEN-DT  | PHOSPHATIDYLINOSITO L4-KINASE ALPHA                            | 1857 1740C>T | S      |
| L36151 | L36151 | 600286 | GEN-DT  | PHOSPHATIDYLINOSITO L4-KINASE ALPHA                            | 2052 1935C>T | S      |
| L36151 | L36151 | 600286 | GEN-DT  | PHOSPHATIDYLINOSITO L4-KINASE ALPHA                            | 2160 2043T>C | S      |
| L36151 | L36151 | 600286 | GEN-DT  | PHOSPHATIDYLINOSITO L4-KINASE ALPHA                            | 2280 2163T>C | S      |
| L36151 | L36151 | 600286 | GEN-DT  | PHOSPHATIDYLINOSITO L4-KINASE ALPHA                            | 2644 2527G>A | D843N  |
| L36151 | L36151 | 600286 | GEN-DT  | PHOSPHATIDYLINOSITO L4-KINASE ALPHA                            | 2749 2632C>A | 3      |
| L36151 | L36151 | 600286 | GEN-DT  | PHOSPHATIDYLINOSITO L4-KINASE ALPHA                            | 2799 2682A>G | 3      |

|        |        |        |             |                                                                                                                 |      |           |       |
|--------|--------|--------|-------------|-----------------------------------------------------------------------------------------------------------------|------|-----------|-------|
| L36151 | L36151 | 600286 | GEN-DT      | L 4-KINASE ALPHA<br>PHOSPHATIDYLINOSITO                                                                         | 2804 | 2687A>G   | 3     |
| L36151 | L36151 | 600286 | GEN-DT      | L 4-KINASE ALPHA<br>PHOSPHATIDYLINOSITO                                                                         | 2844 | 2727C>G   | 3     |
| L36151 | L36151 | 600286 | GEN-DT      | L 4-KINASE ALPHA<br>PHOSPHATIDYLINOSITO                                                                         | 2848 | 2731G>A   | 3     |
| L36151 | L36151 | 600286 | GEN-DT      | L 4-KINASE ALPHA<br>PHOSPHATIDYLINOSITO                                                                         | 2857 | 2740A>G   | 3     |
| L36151 | L36151 | 600286 | GEN-DT      | L 4-KINASE ALPHA<br>PHOSPHATIDYLINOSITO                                                                         | 2877 | 2760A>G   | 3     |
| L36151 | L36151 | 600286 | GEN-DT      | L 4-KINASE ALPHA<br>PHOSPHATIDYLINOSITO                                                                         | 2942 | 2825C>T   | 3     |
| L36566 | L36566 | 601970 | GEN-<br>2N5 | L 4-KINASE ALPHA<br>Human helodermin-<br>preferring VIP receptor<br>(VIP2/PACAP receptor)<br>mRNA, complete cds | 1397 | 1235A>G   | H412R |
| L36566 | L36566 | 601970 | GEN-<br>2N5 | Human helodermin-<br>preferring VIP receptor<br>(VIP2/PACAP receptor)<br>mRNA, complete cds                     | 1440 | 1278A>C   | S     |
| L37792 | L37792 | 186590 | GEN-DX      | mRNA, complete cds                                                                                              | 1337 | 1336A>G   | 3     |
| L41147 | L41147 | 601109 | GEN-2T      | serotonin 1A<br>5-HT6                                                                                           | 287  | (-181)C>T | 5     |
| L42373 | L42373 | 601643 | GEN-<br>2U7 | Homo sapiens<br>phosphatase 2A B56-alpha<br>(PP2A) mRNA, complete<br>cds                                        | 1135 | 564C>T    | S     |
| L42373 | L42373 | 601643 | GEN-<br>2U7 | Homo sapiens<br>phosphatase 2A B56-alpha<br>(PP2A) mRNA, complete<br>cds                                        | 2297 | 1726T>A   | 3     |
| L42373 | L42373 | 601643 | GEN-<br>2U7 | Homo sapiens<br>phosphatase 2A B56-alpha<br>(PP2A) mRNA, complete<br>cds                                        | 2368 | 1797T>C   | 3     |
| L42373 | L42373 | 601643 | GEN-<br>2U7 | Homo sapiens<br>phosphatase 2A B56-alpha<br>(PP2A) mRNA, complete<br>cds                                        | 2782 | 2211G>A   | 3     |
| L42373 | L42373 | 601643 | GEN-<br>2U7 | Homo sapiens<br>phosphatase 2A B56-alpha<br>(PP2A) mRNA, complete<br>cds                                        | 2952 | 2381T>G   | 3     |

|        |        |                                                    |         |                                                                |                     |        |  |
|--------|--------|----------------------------------------------------|---------|----------------------------------------------------------------|---------------------|--------|--|
| 2U7    |        | phosphatase 2A B56-alpha (PP2A) mRNA, complete cds |         |                                                                |                     |        |  |
| L76224 | L76224 | 138254                                             | GEN-3OS | Glutamate Aspartate receptor NMDA 2C                           | 2526 2526G>A        | S      |  |
| L77864 | L77864 | 602709                                             | GEN-3QI | Homo sapiens stat-like protein (Fe65) mRNA, complete cds       | 406 306G>A          | S      |  |
| L77864 | L77864 | 602709                                             | GEN-3QI | Homo sapiens stat-like protein (Fe65) mRNA, complete cds       | 1911 1811G>A        | C604Y  |  |
| L77864 | L77864 | 602709                                             | GEN-3QI | Homo sapiens stat-like protein (Fe65) mRNA, complete cds       | 2639 2539A>C        | 3      |  |
| M10901 | M10901 | 138040                                             | GEN-2W  | Corticosteroid nuclear receptor b                              | 1220 1088A>G        | N363S  |  |
| M10901 | M10901 | 138040                                             | GEN-2W  | Corticosteroid nuclear receptor b                              | 2024 1892-1893AG>AG | S      |  |
| M10901 | M10901 | 138040                                             | GEN-2W  | Corticosteroid nuclear receptor b                              | 2024 1892-1893delAG | F      |  |
| M10901 | M10901 | 138040                                             | GEN-2W  | Corticosteroid nuclear receptor b                              | 2054 1922A>T        | D641V  |  |
| M10901 | M10901 | 138040                                             | GEN-2W  | Corticosteroid nuclear receptor b                              | 2372 2240T>G        | I747S  |  |
| M10901 | M10901 | 138040                                             | GEN-2W  | Corticosteroid nuclear receptor b                              | 2391 2259A>C        | L753F  |  |
| M10901 | M10901 | 138040                                             | GEN-2W  | Corticosteroid nuclear receptor b                              | 2391 2259A>T        | L753F  |  |
| M11050 | M11050 | 138040                                             | GEN-7Y  | Glucocorticoid receptor                                        | 2166 2034C>T        | S      |  |
| M11050 | M11050 | 138040                                             | GEN-7Y  | Glucocorticoid receptor                                        | 3353 3221T>G        | 3      |  |
| M11050 | M11050 | 138040                                             | GEN-7Y  | Glucocorticoid receptor                                        | 3398 3266T>G        | 3      |  |
| M11313 | M11313 | 103950                                             | GEN-E7  | alpha-2-macroglobulin                                          | 1573 1530T>A        | S      |  |
| M11313 | M11313 | 103950                                             | GEN-E7  | alpha-2-macroglobulin                                          | 1799 1756C>T        | F      |  |
| M11313 | M11313 | 103950                                             | GEN-E7  | alpha-2-macroglobulin                                          | 3041 2998G>A        | V1000I |  |
| M11313 | M11313 | 103950                                             | GEN-E7  | alpha-2-macroglobulin                                          | 4474 4431A>C        | 3      |  |
| M12578 | M12578 | 152760                                             | GEN-2Y  | Gonadotropin-releasing hormone (leutinizing-releasing hormone) | 79 47G>C            | W16S   |  |
| M12674 | M12674 | 133430                                             | GEN-7Z  | Estrogen receptor                                              | 1267 975C>G         | S      |  |
| HEXB   | M13519 | 268800                                             | GEN-1OI | Human N-acetyl-beta-                                           | 63 63G>C            | S      |  |

|        |        |        |         |                                                                       |              |       |
|--------|--------|--------|---------|-----------------------------------------------------------------------|--------------|-------|
| HEXB   | M13519 | 268800 | GEN-10I | glucosaminidase (HEXB) mRNA, 3 end                                    | 490 490T>G   | S164A |
| HEXB   | M13519 | 268800 | GEN-10I | Human N-acetyl-beta-glucosaminidase (HEXB) mRNA, 3 end                | 1741 1741A>C | 3     |
| HEXB   | M13519 | 268800 | GEN-10I | Human N-acetyl-beta-glucosaminidase (HEXB) mRNA, 3 end                | 1798 1798A>G | 3     |
| M14113 | M14113 | 306700 | GEN-5T  | Human N-acetyl-beta-glucosaminidase (HEXB) mRNA, 3 end                | 8899 8728G>A | 3     |
| DBI    | M14200 | 125950 | GEN-1QW | Factor VIII Human diazepam binding inhibitor (DBI) mRNA, complete cds | 291 272A>T   | Y91F  |
| M14221 | M14221 | 161565 | GEN-QM  | Human cathepsin B proteinase mRNA, complete cds                       | 184 (-11)T>C | 5     |
| M14221 | M14221 | 161565 | GEN-QM  | Human cathepsin B proteinase mRNA, complete cds                       | 270 76G>C    | V26L  |
| M14221 | M14221 | 161565 | GEN-QM  | Human cathepsin B proteinase mRNA, complete cds                       | 446 252C>T   | S     |
| M14221 | M14221 | 161565 | GEN-QM  | Human cathepsin B proteinase mRNA, complete cds                       | 1254 1060C>G | 3     |
| M14221 | M14221 | 161565 | GEN-QM  | Human cathepsin B proteinase mRNA, complete cds                       | 1306 1112G>A | 3     |
| M14221 | M14221 | 161565 | GEN-QM  | Human cathepsin B proteinase mRNA, complete cds                       | 1336 1142T>A | 3     |
| M14221 | M14221 | 161565 | GEN-QM  | Human cathepsin B proteinase mRNA, complete cds                       | 1338 1144C>T | 3     |
| M14221 | M14221 | 161565 | GEN-QM  | Human cathepsin B proteinase mRNA, complete cds                       | 1451 1257G>A | 3     |
| M14221 | M14221 | 161565 | GEN-QM  | Human cathepsin B proteinase mRNA, complete cds                       | 1462 1268C>T | 3     |



|        |        |        |             |                                                           |              |       |
|--------|--------|--------|-------------|-----------------------------------------------------------|--------------|-------|
| M14221 | M14221 | 161565 | GEN-QM      | Human cathepsin B<br>proteinase mRNA,<br>complete cds     | 1522 1328G>C | 3     |
| M14221 | M14221 | 161565 | GEN-QM      | Human cathepsin B<br>proteinase mRNA,<br>complete cds     | 1557 1363G>C | 3     |
| M14221 | M14221 | 161565 | GEN-QM      | Human cathepsin B<br>proteinase mRNA,<br>complete cds     | 1585 1391C>A | 3     |
| M14221 | M14221 | 161565 | GEN-QM      | Human cathepsin B<br>proteinase mRNA,<br>complete cds     | 1630 1436T>C | 3     |
| M14221 | M14221 | 161565 | GEN-QM      | Human cathepsin B<br>proteinase mRNA,<br>complete cds     | 1668 1474T>G | 3     |
| M14221 | M14221 | 161565 | GEN-QM      | Human cathepsin B<br>proteinase mRNA,<br>complete cds     | 1712 1518C>G | 3     |
| M14221 | M14221 | 161565 | GEN-QM      | Human cathepsin B<br>proteinase mRNA,<br>complete cds     | 1898 1704A>G | 3     |
| M14333 | M14333 | 137025 | GEN-QO      | Homo sapiens c-syn<br>protooncogene mRNA,<br>complete cds | 562 (-18)A>C | 5     |
| M14333 | M14333 | 137025 | GEN-QO      | Homo sapiens c-syn<br>protooncogene mRNA,<br>complete cds | 1647 1068T>C | S     |
| M14333 | M14333 | 137025 | GEN-QO      | Homo sapiens c-syn<br>protooncogene mRNA,<br>complete cds | 2152 1573A>T | T525S |
| ARG1   | M14502 | 207800 | GEN-<br>1RE | Human liver arginase<br>mRNA, complete cds                | 800 744C>T   | S     |
| M14539 | M14539 | 134570 | GEN-QP      | Human factor XIII subunit a<br>mRNA, 3 end                | 1781 1781C>T | P594L |
| M14539 | M14539 | 134570 | GEN-QP      | Human factor XIII subunit a<br>mRNA, 3 end                | 2041 2041C>G | Q681E |
| M14539 | M14539 | 134570 | GEN-QP      | Human factor XIII subunit a<br>mRNA, 3 end                | 2412 2412C>T | 3     |
| M14539 | M14539 | 134570 | GEN-QP      | Human factor XIII subunit a<br>mRNA, 3 end                | 2446 2446G>A | 3     |

|        |        |        |         |                                                       |                    |       |
|--------|--------|--------|---------|-------------------------------------------------------|--------------------|-------|
| M14539 | M14539 | 134570 | GEN-QP  | Human factor XIII subunit a mRNA, 3 end               | 3282 3282G>T       | 3     |
| NGFR   | M14764 | 162010 | GEN-1S8 | Human nerve growth factor receptor mRNA, complete cds | 2716 2603C>T       | 3     |
| NGFR   | M14764 | 162010 | GEN-1S8 | Human nerve growth factor receptor mRNA, complete cds | 2729 2616C>T       | 3     |
| NGFR   | M14764 | 162010 | GEN-1S8 | Human nerve growth factor receptor mRNA, complete cds | 2912 2799G>A       | 3     |
| NGFR   | M14764 | 162010 | GEN-1S8 | Human nerve growth factor receptor mRNA, complete cds | 3252 3139C>G       | 3     |
| M15169 | M15169 | 109690 | GEN-T   | Beta2 Adrenergic Receptor                             | 466 (-1122)C>G     | 5     |
| M15169 | M15169 | 109690 | GEN-T   | Beta2 Adrenergic Receptor                             | 565 (-1023)G>A     | 5     |
| M15169 | M15169 | 109690 | GEN-T   | Beta2 Adrenergic Receptor                             | 1541 (-47)C>T      | 5     |
| M15169 | M15169 | 109690 | GEN-T   | Beta2 Adrenergic Receptor                             | 1633 46A>G         | R16G  |
| M15169 | M15169 | 109690 | GEN-T   | Beta2 Adrenergic Receptor                             | 1633 46A>G         | R16G  |
| M15169 | M15169 | 109690 | GEN-T   | Beta2 Adrenergic Receptor                             | 1666 79C>G         | Q27E  |
| M15169 | M15169 | 109690 | GEN-T   | Beta2 Adrenergic Receptor                             | 1666 79C>G         | Q27E  |
| M15169 | M15169 | 109690 | GEN-T   | Beta2 Adrenergic Receptor                             | 1666 79C>G         | Q27E  |
| M15169 | M15169 | 109690 | GEN-T   | Beta2 Adrenergic Receptor                             | 1687 100G>A        | V34M  |
| M15169 | M15169 | 109690 | GEN-T   | Beta2 Adrenergic Receptor                             | 1839 252G>A        | S     |
| M15169 | M15169 | 109690 | GEN-T   | Beta2 Adrenergic Receptor                             | 2110 523C>A        | S     |
| M15169 | M15169 | 109690 | GEN-T   | Beta2 Adrenergic Receptor                             | 2640 1053G>C       | S     |
| M15169 | M15169 | 109690 | GEN-T   | Beta2 Adrenergic Receptor                             | 2826 1239G>A       | S     |
| M15169 | M15169 | 109690 | GEN-T   | Beta2 Adrenergic Receptor                             | 2862 1275C>G       | 3     |
| M15169 | M15169 | 109690 | GEN-T   | Beta2 Adrenergic Receptor                             | 2864 1277C>A       | 3     |
| M15169 | M15169 | 109690 | GEN-T   | Beta2 Adrenergic Receptor                             | 2865 1278C>A       | 3     |
| M15169 | M15169 | 109690 | GEN-T   | Beta2 Adrenergic Receptor                             | 3371 1784A>T       | 3     |
| M16541 | M16541 | 177400 | GEN-35  | Butyrylcholinesterase                                 | 422 293A>G         | D98G  |
| M16541 | M16541 | 177400 | GEN-35  | Butyrylcholinesterase                                 | 557 428G>A         | G143D |
| M16541 | M16541 | 177400 | GEN-35  | Butyrylcholinesterase                                 | 564 435-436TT>AG>A | F146V |
| M16541 | M16541 | 177400 | GEN-35  | Butyrylcholinesterase                                 | 568 439C>T         | F     |
| M16541 | M16541 | 177400 | GEN-35  | Butyrylcholinesterase                                 | 596 467A>G         | Y156C |

|        |        |        |         |                                                                            |              |        |
|--------|--------|--------|---------|----------------------------------------------------------------------------|--------------|--------|
| M16541 | M16541 | 177400 | GEN-35  | Butyrylcholinesterase                                                      | 941 812C>T   | T271M  |
| M16541 | M16541 | 177400 | GEN-35  | Butyrylcholinesterase                                                      | 961 832A>C   | T278P  |
| M16541 | M16541 | 177400 | GEN-35  | Butyrylcholinesterase                                                      | 978 849G>C   | E283D  |
| M16541 | M16541 | 177400 | GEN-35  | Butyrylcholinesterase                                                      | 1201 1072T>A | L358I  |
| M16541 | M16541 | 177400 | GEN-35  | Butyrylcholinesterase                                                      | 1306 1177G>A | G393R  |
| M16541 | M16541 | 177400 | GEN-35  | Butyrylcholinesterase                                                      | 1382 1253G>T | G418V  |
| M16541 | M16541 | 177400 | GEN-35  | Butyrylcholinesterase                                                      | 1549 1420T>G | F474V  |
| M16541 | M16541 | 177400 | GEN-35  | Butyrylcholinesterase                                                      | 1564 1435G>T | F      |
| M16541 | M16541 | 177400 | GEN-35  | Butyrylcholinesterase                                                      | 1703 1574A>T | E525V  |
| M16541 | M16541 | 177400 | GEN-35  | Butyrylcholinesterase                                                      | 1756 1627C>T | R543C  |
| M16541 | M16541 | 177400 | GEN-35  | Butyrylcholinesterase                                                      | 1828 1699G>A | A567T  |
| M16541 | M16541 | 177400 | GEN-35  | Butyrylcholinesterase                                                      | 1828 1699G>A | A567T  |
| M16541 | M16541 | 177400 | GEN-35  | Butyrylcholinesterase                                                      | 2127 1998A>G | 3      |
| M16541 | M16541 | 177400 | GEN-35  | Butyrylcholinesterase                                                      | 2127 1998A>G | 3      |
| M16765 | M16765 | 104760 | GEN-1YM | Human cerebrovascular and neuritic plaque amyloid beta-protein mRNA, 3 end | 1283 1274A>C | 3      |
| F5     | M16967 | 227400 | GEN-1Z8 | Human coagulation factor V mRNA, complete cds                              | 2391 2301G>A | S      |
| F5     | M16967 | 227400 | GEN-1Z8 | Human coagulation factor V mRNA, complete cds                              | 2663 2573G>A | R858K  |
| F5     | M16967 | 227400 | GEN-1Z8 | Human coagulation factor V mRNA, complete cds                              | 2684 2594G>A | R865H  |
| F5     | M16967 | 227400 | GEN-1Z8 | Human coagulation factor V mRNA, complete cds                              | 5380 5290G>A | V1764M |
| CYP21  | M17252 | 201910 | GEN-201 | Human cytochrome P450c21 mRNA, 3 end                                       | 224 224G>A   | R75H   |
| CYP21  | M17252 | 201910 | GEN-201 | Human cytochrome P450c21 mRNA, 3 end                                       | 330 330C>T   | S      |
| CYP21  | M17252 | 201910 | GEN-201 | Human cytochrome P450c21 mRNA, 3 end                                       | 745 745T>C   | 3      |
| M17262 | M17262 | 176930 | GEN-SM  | Human prothrombin (F2) gene, complete cds, and Alu and KpnI repeats        | 511 480C>T   | S      |
| M20132 | M20132 | 313700 | GEN-38  | Androgen receptor (dihydrotestosterone receptor)                           | 995 633G>A   | S      |
| M20132 | M20132 | 313700 | GEN-38  | Androgen receptor                                                          | 1385 1023T>C | S      |

|         |        |        |         |                                                                                   |                  |       |
|---------|--------|--------|---------|-----------------------------------------------------------------------------------|------------------|-------|
| M20132  | M20132 | 313700 | GEN-38  | (dihydrotestosterone receptor)                                                    | 1786 1424G>A     | G475E |
| M21054  | M21054 | 172410 | GEN-3B  | Androgen receptor (dihydrotestosterone receptor)                                  | 331 294G>A       | S     |
| M21054  | M21054 | 172410 | GEN-3B  | Phospholipase A-2 (PLA-2) lung                                                    | 400 363C>A       | D121E |
| M21551  | M21551 | 162340 | GEN-24P | Human neuromedin B mRNA, complete cds                                             | 252 216C>A       | S     |
| PLA2G2A | M22430 | 172411 | GEN-25V | Human RASF-A PLA2 mRNA, complete cds                                              | 116 (-20)G>T     | 5     |
| PLA2G2A | M22430 | 172411 | GEN-25V | Human RASF-A PLA2 mRNA, complete cds                                              | 231 96G>C        | S     |
| PLA2G2A | M22430 | 172411 | GEN-25V | Human RASF-A PLA2 mRNA, complete cds                                              | 267 132C>T       | S     |
| PLA2G2A | M22430 | 172411 | GEN-25V | Human RASF-A PLA2 mRNA, complete cds                                              | 267 132C>T       | S     |
| PLA2G2A | M22430 | 172411 | GEN-25V | Human RASF-A PLA2 mRNA, complete cds                                              | 278 143-144GT>GT | S     |
| PLA2G2A | M22430 | 172411 | GEN-25V | Human RASF-A PLA2 mRNA, complete cds                                              | 278 143-144delGT | F     |
| PLA2G2A | M22430 | 172411 | GEN-25V | Human RASF-A PLA2 mRNA, complete cds                                              | 643 508C>T       | 3     |
| PLA2G2A | M22430 | 172411 | GEN-25V | Human RASF-A PLA2 mRNA, complete cds                                              | 700 565G>C       | 3     |
| M22538  | M22538 | 600532 | GEN-EO  | NADH dehydrogenase (ubiquinone) flavoprotein 2 (24kD)                             | 219 201A>T       | S     |
| M22538  | M22538 | 600532 | GEN-EO  | NADH dehydrogenase (ubiquinone) flavoprotein 2 (24kD)                             | 469 451G>A       | A151T |
| M22613  | M22613 | 227600 | GEN-3C  | COAGULATION FACTOR X PRECURSOR                                                    | 738 738C>T       | S     |
| M22632  | M22632 | 138150 | GEN-EP  | Glutamic-oxaloacetic transaminase 2, mitochondrial (aspartate aminotransferase 2) | 221 213T>C       | S     |
| M22632  | M22632 | 138150 | GEN-EP  | Glutamic-oxaloacetic transaminase 2,                                              | 236 228T>G       | S     |

|        |        |        |         |                                                                                   |              |       |
|--------|--------|--------|---------|-----------------------------------------------------------------------------------|--------------|-------|
| M22632 | M22632 | 138150 | GEN-EP  | mitochondrial (aspartate aminotransferase 2)                                      | 2009 2001C>T | 3     |
| M24194 | M24194 | None   | GEN-286 | Glutamic-oxaloacetic transaminase 2, mitochondrial (aspartate aminotransferase 2) | 79 (-17)C>A  | 5     |
| M24194 | M24194 | None   | GEN-286 | Human MHC protein homologous to chicken B complex protein mRNA, complete cds      | 102 7G>T     | F     |
| M24194 | M24194 | None   | GEN-286 | Human MHC protein homologous to chicken B complex protein mRNA, complete cds      | 464 369A>T   | S     |
| M24194 | M24194 | None   | GEN-286 | Human MHC protein homologous to chicken B complex protein mRNA, complete cds      | 846 751G>T   | A251S |
| M24194 | M24194 | None   | GEN-286 | Human MHC protein homologous to chicken B complex protein mRNA, complete cds      | 848 753C>T   | S     |
| M24857 | M24857 | 180190 | GEN-80  | Retinoic acid receptor, gamma 1                                                   | 1694 1280C>T | S427L |
| CRYAB  | M24906 | 123590 | GEN-28V | Homo sapiens Rosenthal fiber protein (alpha-B-crystallin) mRNA, 3 end             | 107 107T>G   | V36G  |
| CRYAB  | M24906 | 123590 | GEN-28V | Homo sapiens Rosenthal fiber protein (alpha-B-crystallin) mRNA, 3 end             | 303 303A>T   | 3     |
| CRYAB  | M24906 | 123590 | GEN-28V | Homo sapiens Rosenthal fiber protein (alpha-B-crystallin) mRNA, 3 end             | 305 305G>A   | 3     |
| GAP43  | M25667 | 162060 | GEN-29U | Human neuronal growth protein 43 (GAP-43) mRNA, complete cds                      | 1086 995T>G  | 3     |
| M25756 | M25756 | 118930 | GEN-    | Human secretogranin II                                                            | 855 793G>A   | V265M |

|        |        |        |               |                                                                                                              |              |       |
|--------|--------|--------|---------------|--------------------------------------------------------------------------------------------------------------|--------------|-------|
| M2756  | M2756  | 118930 | 29W<br>GEN-   | gene, complete cds                                                                                           | 899 837C>T   | S     |
| M26383 | M26383 | 146930 | 29W<br>GEN-3E | Human secretogranin II<br>gene, complete cds                                                                 | 259 185C>G   | A62G  |
| M26383 | M26383 | 146930 | GEN-3E        | Interleukin 8                                                                                                | 1237 1163A>T | 3     |
| M26383 | M26383 | 146930 | GEN-3E        | Interleukin 8                                                                                                | 1281 1207A>G | 3     |
| M27436 | M27436 | 134390 | GEN-R7        | Interleukin 8                                                                                                | 1414 1315C>T | 3     |
|        |        |        |               | Human tissue factor gene,<br>complete cds, with a Alu<br>repetitive sequence in the<br>3 untranslated region |              |       |
| M27436 | M27436 | 134390 | GEN-R7        | Human tissue factor gene,<br>complete cds, with a Alu<br>repetitive sequence in the<br>3 untranslated region | 1508 1409A>G | 3     |
| M27436 | M27436 | 134390 | GEN-R7        | Human tissue factor gene,<br>complete cds, with a Alu<br>repetitive sequence in the<br>3 untranslated region | 1588 1489T>G | 3     |
| M27492 | M27492 | 147810 | GEN-3F        | Human tissue factor gene,<br>complete cds, with a Alu<br>repetitive sequence in the<br>3 untranslated region | 4686 4604T>G | 3     |
|        |        |        |               | INTERLEUKIN 1<br>RECEPTOR, TYPE I<br>PRECURSOR                                                               |              |       |
| M27875 | M27875 | 107680 | GEN-<br>2CK   | Human apolipoprotein A-I<br>mRNA, complete cds                                                               | 34 15G>C     | S     |
| M27875 | M27875 | 107680 | GEN-<br>2CK   | Human apolipoprotein A-I<br>mRNA, complete cds                                                               | 202 183C>T   | S     |
| M27875 | M27875 | 107680 | GEN-<br>2CK   | Human apolipoprotein A-I<br>mRNA, complete cds                                                               | 204 185T>G   | L62W  |
| M27875 | M27875 | 107680 | GEN-<br>2CK   | Human apolipoprotein A-I<br>mRNA, complete cds                                                               | 255 236C>T   | S79F  |
| M27875 | M27875 | 107680 | GEN-<br>2CK   | Human apolipoprotein A-I<br>mRNA, complete cds                                                               | 689 670C>T   | S     |
| M27875 | M27875 | 107680 | GEN-<br>2CK   | Human apolipoprotein A-I<br>mRNA, complete cds                                                               | 824 805G>A   | 3     |
| M28211 | M28211 | 179511 | GEN-<br>2D1   | Human apolipoprotein A-I<br>mRNA, complete cds                                                               | 677 607A>G   | T203A |
|        |        |        |               | Homo sapiens GTP-<br>binding protein (RAB4)                                                                  |              |       |
| M28211 | M28211 | 179511 | GEN-<br>2D1   | mRNA, complete cds                                                                                           | 679 609C>A   | S     |
|        |        |        |               | Homo sapiens GTP-<br>binding protein (RAB4)                                                                  |              |       |
| M28215 | M28215 | 179512 | GEN-<br>2D3   | mRNA, complete cds                                                                                           | 297 241G>C   | G81R  |
|        |        |        |               | Homo sapiens GTP-<br>binding protein (RAB5)                                                                  |              |       |

|        |        |        |         |                                                                          |              |       |
|--------|--------|--------|---------|--------------------------------------------------------------------------|--------------|-------|
| POMC   | M28636 | 17830  | GEN-2DG | mRNA, complete cds<br>Adrenocorticotrophic hormone (ACTH)                | 92 92C>T     | 3     |
| CETP   | M30185 | 118470 | GEN-2FK | Human cholesteryl ester transfer protein mRNA, complete cds              | 1283 1153G>C | V385L |
| CETP   | M30185 | 118470 | GEN-2FK | Human cholesteryl ester transfer protein mRNA, complete cds              | 1298 1168G>C | A390P |
| CETP   | M30185 | 118470 | GEN-2FK | Human cholesteryl ester transfer protein mRNA, complete cds              | 1394 1264A>G | I422V |
| CETP   | M30185 | 118470 | GEN-2FK | Human cholesteryl ester transfer protein mRNA, complete cds              | 1394 1264A>G | I422V |
| CETP   | M30185 | 118470 | GEN-2FK | Human cholesteryl ester transfer protein mRNA, complete cds              | 1506 1376A>G | D459G |
| CETP   | M30185 | 118470 | GEN-2FK | Human cholesteryl ester transfer protein mRNA, complete cds              | 1696 1566G>A | 3     |
| M30262 | M30262 | 600295 | GEN-WA  | Human cardiolipin-atrial natriuretic factor (CDD-ANF) mRNA, complete cds | 178 79C>T    | P27S  |
| M30262 | M30262 | 600295 | GEN-WA  | Human cardiolipin-atrial natriuretic factor (CDD-ANF) mRNA, complete cds | 203 104C>G   | A35G  |
| M30262 | M30262 | 600295 | GEN-WA  | Human cardiolipin-atrial natriuretic factor (CDD-ANF) mRNA, complete cds | 210 111G>T   | S     |
| M30262 | M30262 | 600295 | GEN-WA  | Human cardiolipin-atrial natriuretic factor (CDD-ANF) mRNA, complete cds | 327 228C>T   | S     |
| M30262 | M30262 | 600295 | GEN-WA  | Human cardiolipin-atrial natriuretic factor (CDD-ANF) mRNA, complete cds | 553 454T>C   | F     |
| M30262 | M30262 | 600295 | GEN-WA  | Human cardiolipin-atrial natriuretic factor (CDD-ANF) mRNA, complete cds | 626 527G>T   | 3     |
| M30262 | M30262 | 600295 | GEN-WA  | Human cardiolipin-atrial natriuretic factor (CDD-ANF) mRNA, complete cds | 640 541T>C   | 3     |

|        |        |        |        |                                                                    |              |       |
|--------|--------|--------|--------|--------------------------------------------------------------------|--------------|-------|
| M31328 | M31328 | 139130 | GEN-7G | ANF) mRNA, complete cds                                            | 1049 1043G>A | 3     |
| M32313 | M32313 | 184753 | GEN-5Y | Guanine nucleotide binding protein (G protein), beta polypeptide 3 | 1271 1241C>T | 3     |
| M32313 | M32313 | 184753 | GEN-5Y | Steroid 5 alpha reductase 1                                        | 1344 1314G>A | 3     |
| M32313 | M32313 | 184753 | GEN-5Y | Steroid 5 alpha reductase 1                                        | 1489 1459G>A | 3     |
| M32313 | M32313 | 184753 | GEN-5Y | Steroid 5 alpha reductase 1                                        | 1780 1750T>C | 3     |
| M32315 | M32315 | 191191 | GEN-3M | Tumor necrosis factor receptor 2 (75kD)                            | 676 587T>G   | M196R |
| M32315 | M32315 | 191191 | GEN-3M | Tumor necrosis factor receptor 2 (75kD)                            | 1176 1087G>A | A363T |
| M32315 | M32315 | 191191 | GEN-3M | Tumor necrosis factor receptor 2 (75kD)                            | 1668 1579G>T | 3     |
| M32315 | M32315 | 191191 | GEN-3M | Tumor necrosis factor receptor 2 (75kD)                            | 2898 2809G>A | 3     |
| M32315 | M32315 | 191191 | GEN-3M | Tumor necrosis factor receptor 2 (75kD)                            | 3671 3582G>A | 3     |
| M34479 | M34479 | 179060 | GEN-F9 | Pyruvate dehydrogenase (lipoamide) beta                            | 109 109G>A   | D37N  |
| M34479 | M34479 | 179060 | GEN-F9 | Pyruvate dehydrogenase (lipoamide) beta                            | 438 438A>G   | S     |
| M34479 | M34479 | 179060 | GEN-F9 | Pyruvate dehydrogenase (lipoamide) beta                            | 1172 1172A>C | 3     |
| M34479 | M34479 | 179060 | GEN-F9 | Pyruvate dehydrogenase (lipoamide) beta                            | 1179 1179C>T | 3     |
| M34479 | M34479 | 179060 | GEN-F9 | Pyruvate dehydrogenase (lipoamide) beta                            | 1323 1323C>A | 3     |
| M34479 | M34479 | 179060 | GEN-F9 | Pyruvate dehydrogenase (lipoamide) beta                            | 1376 1376G>C | 3     |
| M34479 | M34479 | 179060 | GEN-F9 | Pyruvate dehydrogenase (lipoamide) beta                            | 1433 1433C>T | 3     |
| M34539 | M34539 | 186945 | GEN-3N | FKBP, tacrolimus binding protein, FK506-binding protein 1 (12kD)   | 449 371A>G   | 3     |
| M34539 | M34539 | 186945 | GEN-3N | FKBP, tacrolimus binding protein, FK506-binding protein            | 486 408G>A   | 3     |



|        |        |        |         |                                                                                            |              |       |
|--------|--------|--------|---------|--------------------------------------------------------------------------------------------|--------------|-------|
| M34539 | M34539 | 186945 | GEN-3N  | protein 1 (12kD)<br>FKBP, tacrolimus binding<br>protein, FK506-binding<br>protein 1 (12kD) | 650 572T>C   | 3     |
| M36035 | M36035 | 109610 | GEN-3P  | Benzodiazepine receptor,<br>peripheral-type                                                | 500 439G>A   | A147T |
| M36035 | M36035 | 109610 | GEN-3P  | Benzodiazepine receptor,<br>peripheral-type                                                | 500 439G>A   | A147T |
| M36035 | M36035 | 109610 | GEN-3P  | Benzodiazepine receptor,<br>peripheral-type                                                | 546 485A>G   | H162R |
| M36035 | M36035 | 109610 | GEN-3P  | Benzodiazepine receptor,<br>peripheral-type                                                | 546 485A>G   | H162R |
| M36035 | M36035 | 109610 | GEN-3P  | Benzodiazepine receptor,<br>peripheral-type                                                | 711 650T>G   | 3     |
| M37400 | M37400 | 138180 | GEN-FC  | Glutamic-oxaloacetic<br>transaminase 1, soluble<br>(aspartate<br>aminotransferase 1)       | 1588 1564A>C | 3     |
| M37400 | M37400 | 138180 | GEN-FC  | Glutamic-oxaloacetic<br>transaminase 1, soluble<br>(aspartate<br>aminotransferase 1)       | 1810 1786G>A | 3     |
| M55040 | M55040 | 100740 | GEN-3Q  | acetylcholinesterase                                                                       | 323 167C>T   | P56L  |
| M55040 | M55040 | 100740 | GEN-3Q  | acetylcholinesterase                                                                       | 1154 998T>A  | V333E |
| M55040 | M55040 | 100740 | GEN-3Q  | acetylcholinesterase                                                                       | 1213 1057C>A | H353N |
| M55040 | M55040 | 100740 | GEN-3Q  | acetylcholinesterase                                                                       | 1482 1326G>T | S     |
| M55040 | M55040 | 100740 | GEN-3Q  | acetylcholinesterase                                                                       | 1587 1431C>T | S     |
| M55040 | M55040 | 100740 | GEN-3Q  | acetylcholinesterase                                                                       | 1587 1431C>T | S     |
| M55040 | M55040 | 100740 | GEN-3Q  | acetylcholinesterase                                                                       | 1663 1507T>C | F503L |
| M57414 | M57414 | None   | GEN-4FK | Human neurokinin A<br>receptor (NK-2R) mRNA,<br>complete cds                               | 68 68T>C     | I23T  |
| M57414 | M57414 | None   | GEN-4FK | Human neurokinin A<br>receptor (NK-2R) mRNA,<br>complete cds                               | 951 951G>A   | S     |
| M57414 | M57414 | None   | GEN-4FK | Human neurokinin A<br>receptor (NK-2R) mRNA,<br>complete cds                               | 1171 1171C>G | P391A |
| M58525 | M58525 | 116790 | GEN-3S  | Catechol-O-<br>methyltransferase                                                           | 390 186T>C   | S     |

|        |        |        |         |                                                                                         |                           |       |
|--------|--------|--------|---------|-----------------------------------------------------------------------------------------|---------------------------|-------|
| M58525 | M58525 | 116790 | GEN-3S  | Catechol-O-methyltransferase                                                            | 390 186T>C                | S     |
| M58525 | M58525 | 116790 | GEN-3S  | Catechol-O-methyltransferase                                                            | 418 214G>T                | A72S  |
| M58525 | M58525 | 116790 | GEN-3S  | Catechol-O-methyltransferase                                                            | 423 219G>A                | S     |
| M58525 | M58525 | 116790 | GEN-3S  | Catechol-O-methyltransferase                                                            | 612 408C>G                | S     |
| M58525 | M58525 | 116790 | GEN-3S  | Catechol-O-methyltransferase                                                            | 676 472A>G                | M158V |
| M58525 | M58525 | 116790 | GEN-3S  | Catechol-O-methyltransferase                                                            | 676 472A>G                | M158V |
| M58525 | M58525 | 116790 | GEN-3S  | Catechol-O-methyltransferase                                                            | 813 609C>T                | S     |
| M58525 | M58525 | 116790 | GEN-3S  | Catechol-O-methyltransferase                                                            | 1031 827delC              | F     |
| M58525 | M58525 | 116790 | GEN-3S  | Catechol-O-methyltransferase                                                            | 1039 835C>A               | 3     |
| M59305 | M59305 | 108962 | GEN-39P | Human atrial natriuretic peptide clearance receptor (ANP C-receptor) mRNA, complete cds | 160 (-203)-(-199)delTTTTT | F     |
| M59979 | M59979 | 176805 | GEN-Z   | Cyclooxygenase 1 COX1                                                                   | 644 639C>A                | S     |
| M59979 | M59979 | 176805 | GEN-Z   | Cyclooxygenase 1 COX1                                                                   | 1892 1887C>A              | 3     |
| M59979 | M59979 | 176805 | GEN-Z   | Cyclooxygenase 1 COX1                                                                   | 2030 2025G>A              | 3     |
| TCN2   | M60396 | 275350 | GEN-3AX | Human transcobalamin II (TCII) mRNA, complete cds                                       | 1164 1127C>T              | S376L |
| TCN2   | M60396 | 275350 | GEN-3AX | Human transcobalamin II (TCII) mRNA, complete cds                                       | 1765 1728T>C              | 3     |
| M60857 | M60857 | 123841 | GEN-10  | Cyclophilin B                                                                           | 183 171C>T                | S     |
| M60857 | M60857 | 123841 | GEN-10  | Cyclophilin B                                                                           | 217 205G>T                | V69L  |
| M60857 | M60857 | 123841 | GEN-10  | Cyclophilin B                                                                           | 702 690C>T                | 3     |
| M60857 | M60857 | 123841 | GEN-10  | Cyclophilin B                                                                           | 804 792A>C                | 3     |
| M62762 | M62762 | 108745 | GEN-FP  | Vacuolar H+ ATPase proton channel subunit                                               | 425 195C>T                | S     |
| M62762 | M62762 | 108745 | GEN-FP  | Vacuolar H+ ATPase proton channel subunit                                               | 784 554C>G                | 3     |
| M62762 | M62762 | 108745 | GEN-FP  | Vacuolar H+ ATPase proton channel subunit                                               | 838 608C>T                | 3     |

|             |        |        |         |                                                                                                      |              |       |
|-------------|--------|--------|---------|------------------------------------------------------------------------------------------------------|--------------|-------|
| LRPAP1      | M63959 | 104225 | GEN-3EI | proton channel subunit<br>Human alpha-2-macroglobulin receptor-associated protein mRNA, complete cds | 850 837G>A   | S     |
| LRPAP1      | M63959 | 104225 | GEN-3EI | Human alpha-2-macroglobulin receptor-associated protein mRNA, complete cds                           | 1093 1080C>T | 3     |
| LRPAP1      | M63959 | 104225 | GEN-3EI | Human alpha-2-macroglobulin receptor-associated protein mRNA, complete cds                           | 1249 1236C>T | 3     |
| FGFR3       | M64347 | 134934 | GEN-3EX | Human novel growth factor receptor mRNA, 3 cds                                                       | 3108 3108C>A | 3     |
| FGFR3       | M64347 | 134934 | GEN-3EX | Human novel growth factor receptor mRNA, 3 cds                                                       | 3715 3715G>A | 3     |
| M64590      | M64590 | 238300 | GEN-FU  | Glycine cleavage system: Protein P                                                                   | 3076 2926A>G | M976V |
| M64799      | M64799 | None   | GEN-4DN | Histamine receptor H2                                                                                | 398 398T>C   | V133A |
| M64799      | M64799 | None   | GEN-4DN | Histamine receptor H2                                                                                | 525 525A>T   | K175N |
| M64799      | M64799 | None   | GEN-4DN | Histamine receptor H2                                                                                | 620 620A>G   | K207R |
| M64799      | M64799 | None   | GEN-4DN | Histamine receptor H2                                                                                | 649 649A>G   | N217D |
| M64799      | M64799 | None   | GEN-4DN | Histamine receptor H2                                                                                | 692 692A>G   | K231R |
| M64799      | M64799 | None   | GEN-4DN | Histamine receptor H2                                                                                | 802 802G>A   | V268M |
| PRKAR1<br>B | M65066 | 176911 | GEN-3FK | Human cAMP-dependent protein kinase regulatory subunit RI-beta mRNA, 3 end                           | 1424 1424C>G | 3     |
| PRKAR1<br>B | M65066 | 176911 | GEN-3FK | Human cAMP-dependent protein kinase regulatory subunit RI-beta mRNA, 3 end                           | 1514 1514G>C | 3     |
| PRKAR1<br>B | M65066 | 176911 | GEN-3FK | Human cAMP-dependent protein kinase regulatory                                                       | 1550 1550G>C | 3     |

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|             |        |        |         |                                                                            |              |       |
|-------------|--------|--------|---------|----------------------------------------------------------------------------|--------------|-------|
| PRKAR1<br>B | M65066 | 176911 | GEN-3FK | subunit RI-beta mRNA, 3 end                                                | 1862 1862G>A | 3     |
| PRKAR1<br>B | M65066 | 176911 | GEN-3FK | Human cAMP-dependent protein kinase regulatory subunit RI-beta mRNA, 3 end | 2139 2139C>T | 3     |
| FSHR        | M65085 | 136435 | GEN-3FQ | FSH receptor                                                               | 2105 2039G>A | S680N |
| EDN2        | M65199 | 131241 | GEN-CBS | Endothelin 2                                                               | 384 314C>T   | A105V |
| EDN2        | M65199 | 131241 | GEN-CBS | Endothelin 2                                                               | 997 927A>G   | 3     |
| EDN2        | M65199 | 131241 | GEN-CBS | Endothelin 2                                                               | 997 927A>G   | 3     |
| M67439      | M67439 | 126453 | GEN-4EI | Dopamine Receptor D5                                                       | 1500 1353T>A | S     |
| M67439      | M67439 | 126453 | GEN-4EI | Dopamine Receptor D5                                                       | 1512 1365G>A | F     |
| M67439      | M67439 | 126453 | GEN-4EI | Dopamine Receptor D5                                                       | 1566 1419G>A | S     |
| M69175      | M69175 | 238330 | GEN-FX  | Glycine cleavage system: Protein H                                         | 710 686C>G   | 3     |
| M69175      | M69175 | 238330 | GEN-FX  | Glycine cleavage system: Protein H                                         | 710 686C>G   | 3     |
| M69175      | M69175 | 238330 | GEN-FX  | Glycine cleavage system: Protein H                                         | 737 713C>T   | 3     |
| M69175      | M69175 | 238330 | GEN-FX  | Glycine cleavage system: Protein H                                         | 1007 983C>T  | 3     |
| M69226      | M69226 | 309850 | GEN-3Z  | Monoamine oxidase A                                                        | 435 385A>C   | S     |
| M69226      | M69226 | 309850 | GEN-3Z  | Monoamine oxidase A                                                        | 936 886C>T   | F     |
| M69226      | M69226 | 309850 | GEN-3Z  | Monoamine oxidase A                                                        | 941 891T>G   | S     |
| M69226      | M69226 | 309850 | GEN-3Z  | Monoamine oxidase A                                                        | 941 891T>G   | S     |
| M69226      | M69226 | 309850 | GEN-3Z  | Monoamine oxidase A                                                        | 1076 1026A>T | S     |
| M69226      | M69226 | 309850 | GEN-3Z  | Monoamine oxidase A                                                        | 1373 1323G>A | F     |
| M69226      | M69226 | 309850 | GEN-3Z  | Monoamine oxidase A                                                        | 1460 1410C>T | S     |
| M69226      | M69226 | 309850 | GEN-3Z  | Monoamine oxidase A                                                        | 1460 1410C>T | S     |
| M69226      | M69226 | 309850 | GEN-3Z  | Monoamine oxidase A                                                        | 1609 1559A>G | K520R |
| SRD5A2      | M74047 | 264600 | GEN-    | Human steroid 5-alpha-                                                     | 2379 2352A>G | 3     |

|        |        |        |         |                                                                                                       |               |       |
|--------|--------|--------|---------|-------------------------------------------------------------------------------------------------------|---------------|-------|
| GALN   | M77140 | 137035 | CDC     | reductase 2 (SRD5A2)<br>mRNA, complete cds                                                            | 339 339C>T    | 3     |
|        |        |        | GEN-3PM | H.sapiens pro-galanin mRNA, 3 end                                                                     |               |       |
| M80646 | M80646 | 274180 | GEN-40  | Thromboxane synthase                                                                                  | 756 585G>C    | S     |
| M80646 | M80646 | 274180 | GEN-40  | Thromboxane synthase                                                                                  | 1240 1069C>G  | L357V |
| M81590 | M81590 | 182131 | GEN-3VZ | Serotonin 5-HT receptors                                                                              | 190 129C>T    | S     |
|        |        |        | GEN-3VZ | 5-HT1D                                                                                                |               |       |
| M81590 | M81590 | 182131 | GEN-3VZ | Serotonin 5-HT receptors                                                                              | 432 371T>G    | F124C |
|        |        |        | GEN-3VZ | 5-HT1D                                                                                                |               |       |
| M81590 | M81590 | 182131 | GEN-3VZ | Serotonin 5-HT receptors                                                                              | 922 861G>C    | S     |
|        |        |        | GEN-3VZ | 5-HT1D                                                                                                |               |       |
| M81590 | M81590 | 182131 | GEN-3VZ | Serotonin 5-HT receptors                                                                              | 1241 1180G>A  | 3     |
|        |        |        | GEN-3VZ | 5-HT1D                                                                                                |               |       |
| TAC1R  | M81797 | 162323 | GEN-3W8 | Tachylinins NK1 receptor                                                                              | 696 652G>A    | V218I |
|        |        |        | GEN-3W8 |                                                                                                       |               |       |
| TAC1R  | M81797 | 162323 | GEN-3W8 | Tachylinins NK1 receptor                                                                              | 1397 1353G>C  | 3     |
|        |        |        | GEN-42  | Glutamate decarboxylase 1 (brain, 67kD)                                                               | 424 (-127)G>A | 5     |
| M81883 | M81883 | 266100 | GEN-42  | Glutamate decarboxylase 1 (brain, 67kD)                                                               | 597 47G>A     | G16E  |
| M81883 | M81883 | 266100 | GEN-42  | Glutamate decarboxylase 1 (brain, 67kD)                                                               | 599 49G>C     | A17P  |
| M81883 | M81883 | 266100 | GEN-42  | Glutamate decarboxylase 1 (brain, 67kD)                                                               | 661 111T>C    | S     |
| M81883 | M81883 | 266100 | GEN-42  | Glutamate decarboxylase 1 (brain, 67kD)                                                               | 1042 492C>T   | S     |
| M81883 | M81883 | 266100 | GEN-42  | Glutamate decarboxylase 1 (brain, 67kD)                                                               | 2005 1455A>G  | S     |
| M81883 | M81883 | 266100 | GEN-42  | Glutamate decarboxylase 1 (brain, 67kD)                                                               | 3033 2483C>T  | 3     |
| M81883 | M81883 | 266100 | GEN-42  | Glutamate decarboxylase 1 (brain, 67kD)                                                               | 2316 2307T>G  | 3     |
| M82962 | M82962 | 600388 | GEN-3XC | Human N-benzoyl-L-tyrosyl-p-amino-benzoic acid hydrolase alpha subunit (PPH alpha) mRNA, complete cds |               |       |
|        |        |        | GEN-3XC | Human N-benzoyl-L-tyrosyl-p-amino-benzoic acid hydrolase alpha subunit (PPH alpha)                    |               |       |
| M82962 | M82962 | 600388 | GEN-3XC | Human N-benzoyl-L-tyrosyl-p-amino-benzoic acid hydrolase alpha subunit (PPH alpha)                    | 2428 2419A>C  | 3     |

|        |        |        |         |                                                                                                                    |              |       |
|--------|--------|--------|---------|--------------------------------------------------------------------------------------------------------------------|--------------|-------|
| M83566 | M83566 | 114206 | GEN-3Y7 | mRNA, complete cds<br>Human<br>neuroendocrine/beta-cell-type calcium channel<br>alpha-1 subunit mRNA, complete cds | 1222 1104C>T | S     |
| M83566 | M83566 | 114206 | GEN-3Y7 | Human<br>neuroendocrine/beta-cell-type calcium channel<br>alpha-1 subunit mRNA, complete cds                       | 1468 1350G>A | S     |
| CHRNA5 | M83712 | 118505 | GEN-3YQ | Nicotinic, Cholinergic receptor alpha 5                                                                            | 1340 1192G>A | D398N |
| M84755 | M84755 | 162641 | GEN-46  | Neuropeptide Y1                                                                                                    | 1121 1121A>C | K374T |
| TGFBR2 | M85079 | 190182 | GEN-3ZS | Human TGF-beta type II receptor mRNA, complete cds                                                                 | 2045 1710A>C | 3     |
| YWHAZ  | M86400 | 601288 | GEN-40Y | Human phospholipase A2 mRNA, complete cds                                                                          | 1653 1569T>A | 3     |
| YWHAZ  | M86400 | 601288 | GEN-40Y | Human phospholipase A2 mRNA, complete cds                                                                          | 2599 2515C>G | 3     |
| YWHAZ  | M86400 | 601288 | GEN-40Y | Human phospholipase A2 mRNA, complete cds                                                                          | 2619 2535A>C | 3     |
| YWHAZ  | M86400 | 601288 | GEN-40Y | Human phospholipase A2 mRNA, complete cds                                                                          | 2656 2572A>C | 3     |
| YWHAZ  | M86400 | 601288 | GEN-40Y | Human phospholipase A2 mRNA, complete cds                                                                          | 2745 2661C>T | 3     |
| YWHAZ  | M86400 | 601288 | GEN-40Y | Human phospholipase A2 mRNA, complete cds                                                                          | 2761 2677A>C | 3     |
| GABRR2 | M86868 | 137162 | GEN-4FS | Gamma-aminobutyric acid (GABA) A receptor                                                                          | 1369 1289C>T | T430M |
| M87290 | M87290 | 106165 | GEN-19  | Angiotensin receptor AT1                                                                                           | 296 16T>C    | S6P   |
| M87290 | M87290 | 106165 | GEN-19  | Angiotensin receptor AT1                                                                                           | 413 133G>A   | G45R  |
| M87290 | M87290 | 106165 | GEN-19  | Angiotensin receptor AT1                                                                                           | 853 573T>C   | S     |
| M87290 | M87290 | 106165 | GEN-19  | Angiotensin receptor AT1                                                                                           | 853 573T>C   | S     |
| M87290 | M87290 | 106165 | GEN-19  | Angiotensin receptor AT1                                                                                           | 1342 1062A>G | S     |
| M87290 | M87290 | 106165 | GEN-19  | Angiotensin receptor AT1                                                                                           | 1342 1062A>G | S     |
| M87290 | M87290 | 106165 | GEN-19  | Angiotensin receptor AT1                                                                                           | 1430 1150T>G | 3     |
| M87290 | M87290 | 106165 | GEN-19  | Angiotensin receptor AT1                                                                                           | 1446 1166C>A | 3     |

|        |        |        |         |                                                       |                        |        |
|--------|--------|--------|---------|-------------------------------------------------------|------------------------|--------|
| M87290 | M87290 | 106165 | GEN-19  | Angiotensin receptor AT1                              | 1446 1166C>A           | 3      |
| M87290 | M87290 | 106165 | GEN-19  | Angiotensin receptor AT1                              | 1446 1166C>A           | 3      |
| M87290 | M87290 | 106165 | GEN-19  | Angiotensin receptor AT1                              | 1453 1173A>G           | 3      |
| M87290 | M87290 | 106165 | GEN-19  | Angiotensin receptor AT1                              | 1677 1397G>A           | 3      |
| M87290 | M87290 | 106165 | GEN-19  | Angiotensin receptor AT1                              | 1797 1517G>T           | 3      |
| M87290 | M87290 | 106165 | GEN-19  | Angiotensin receptor AT1                              | 1885 1605C>T           | 3      |
| M87290 | M87290 | 106165 | GEN-19  | Angiotensin receptor AT1                              | 1916 1636T>C           | 3      |
| M87290 | M87290 | 106165 | GEN-19  | Angiotensin receptor AT1                              | 2158 1878A>G           | 3      |
| M87290 | M87290 | 106165 | GEN-19  | Angiotensin receptor AT1                              | 1614 1471T>C           | 3      |
| M89473 | M89473 | None   | GEN-4FU | NEUROMEDIN K RECEPTOR                                 |                        |        |
| M90100 | M90100 | 600262 | GEN-1A  | Cyclooxygenase 2 COX2                                 | 2159 2062G>C           | 3      |
| M90100 | M90100 | 600262 | GEN-1A  | Cyclooxygenase 2 COX2                                 | 2186 2089-2094ATATTA   | 3      |
| M90100 | M90100 | 600262 | GEN-1A  | Cyclooxygenase 2 COX2                                 | 2186 2089->ATATTA      | 3      |
| M90100 | M90100 | 600262 | GEN-1A  | Cyclooxygenase 2 COX2                                 | 2186 2089-2094deATATTA | 3      |
| M90100 | M90100 | 600262 | GEN-1A  | Cyclooxygenase 2 COX2                                 | 2230 2133A>G           | 3      |
| M90100 | M90100 | 600262 | GEN-1A  | Cyclooxygenase 2 COX2                                 | 2339 2242T>C           | 3      |
| M90100 | M90100 | 600262 | GEN-1A  | Cyclooxygenase 2 COX2                                 | 2409 2312G>A           | 3      |
| M90100 | M90100 | 600262 | GEN-1A  | Cyclooxygenase 2 COX2                                 | 2726 2629C>T           | 3      |
| M90100 | M90100 | 600262 | GEN-1A  | Cyclooxygenase 2 COX2                                 | 2983 2886C>T           | 3      |
| M92269 | M92269 | 114205 | GEN-SV  | Ca Channel alpha1c (alt. splice) L-Type               | 3846 3846C>T           | S      |
| M92269 | M92269 | 114205 | GEN-SV  | Ca Channel alpha1c (alt. splice) L-Type               | 5505 5505G>A           | S      |
| M92269 | M92269 | 114205 | GEN-SV  | Ca Channel alpha1c (alt. splice) L-Type               | 6582 6582A>G           | S      |
| M92269 | M92269 | 114205 | GEN-SV  | Ca Channel alpha1c (alt. splice) L-Type               | 6613 6613G>C           | G2205R |
| M92269 | M92269 | 114205 | GEN-SV  | Ca Channel alpha1c (alt. splice) L-Type               | 6614 6614G>C           | G2205A |
| M93415 | M93415 | 102581 | GEN-48S | Human activin type II receptor mRNA, complete cds     | 136 (-38)G>T           | 5      |
| M94055 | M94055 | 601219 | GEN-493 | Human voltage-gated sodium channel mRNA, complete cds | 5226 5121G>A           | S      |
| IL8RB  | M94582 | 146928 | GEN-    | Interleukin 8 receptor                                | 838 786T>C             | S      |

|             |        |        |                    |                                                                                 |              |       |
|-------------|--------|--------|--------------------|---------------------------------------------------------------------------------|--------------|-------|
| IL8RB       | M94582 | 146928 | 49G<br>GEN-<br>49G | Interleukin 8 receptor                                                          | 1262 1210C>T | 3     |
| IL8RB       | M94582 | 146928 | 49G<br>GEN-<br>49G | Interleukin 8 receptor                                                          | 1494 1442A>G | 3     |
| M98045      | M98045 | 136510 | 4C3<br>GEN-<br>4C3 | Homo sapiens<br>folypolyglutamate<br>synthetase mRNA,<br>complete cds           | 802 732C>T   | S     |
| M98045      | M98045 | 136510 | 4C3<br>GEN-<br>4C3 | Homo sapiens<br>folypolyglutamate<br>synthetase mRNA,<br>complete cds           | 1747 1677G>T | 3     |
| M98045      | M98045 | 136510 | 4C3<br>GEN-<br>4C3 | Homo sapiens<br>folypolyglutamate<br>synthetase mRNA,<br>complete cds           | 1900 1830T>C | 3     |
| M98045      | M98045 | 136510 | 4C3<br>GEN-<br>4C3 | Homo sapiens<br>folypolyglutamate<br>synthetase mRNA,<br>complete cds           | 1900 1830T>C | 3     |
| M98045      | M98045 | 136510 | 4C3<br>GEN-<br>4C3 | Homo sapiens<br>folypolyglutamate<br>synthetase mRNA,<br>complete cds           | 1912 1842G>A | 3     |
| M98045      | M98045 | 136510 | 4C3<br>GEN-<br>4C3 | Homo sapiens<br>folypolyglutamate<br>synthetase mRNA,<br>complete cds           | 1995 1925C>G | 3     |
| M98539      | M98539 | 176803 | GEN-SW             | prostaglandin D2 synthase<br>gene                                               | 157 158C>A   | 3     |
| S63912      | S63912 | 601233 | GEN-<br>3EJ        | D10S102=FBRNP [human,<br>fetal brain, mRNA, 3043 nt]                            | 2193 2163G>A | 3     |
| GABRB2      | S77553 | 600232 | GEN-<br>4FO        | Gamma-aminobutyric acid<br>(GABA) A receptor                                    | 438 438C>G   | S     |
| ADCYAP<br>1 | S83513 | 102980 | GEN-<br>3YA        | pituitary adenylate cyclase<br>activating polypeptide<br>[human, mRNA, 1940 nt] | 1521 1520G>A | 3     |
| U00672      | U00672 | 146933 | GEN-4A             | Interleukin 10 receptor                                                         | 3377 3316A>C | 3     |
| U00672      | U00672 | 146933 | GEN-4A             | Interleukin 10 receptor                                                         | 3524 3463A>G | 3     |
| GLP1R       | U01157 | 138032 | GEN-V3             | Human glucagon-like                                                             | 780 780C>A   | F260L |



|        |        |        |         |                                                                                                                                 |              |       |
|--------|--------|--------|---------|---------------------------------------------------------------------------------------------------------------------------------|--------------|-------|
| GLP1R  | U01157 | 138032 | GEN-V3  | peptide-1 receptor mRNA<br>with CA dinucleotide<br>repeat, complete cds                                                         | 947 947G>C   | G316A |
| GLP1R  | U01157 | 138032 | GEN-V3  | Human glucagon-like<br>peptide-1 receptor mRNA<br>with CA dinucleotide<br>repeat, complete cds                                  | 1200 1200C>A | S     |
| U02326 | U02326 | 142445 | GEN-PE  | Human glucagon-like<br>peptide-1 receptor mRNA<br>with CA dinucleotide<br>repeat, complete cds                                  | 752 644G>A   | G215E |
| SLO    | U02632 | 600150 | GEN-XA  | Human clone ndf43 neu<br>differentiation factor<br>mRNA, complete cds                                                           | 2377 2377T>G | S793A |
| U02882 | U02882 | 600129 | GEN-XU  | Calcium-activated<br>potassium channel<br>Human rolipram-sensitive<br>3,5-cyclic AMP<br>phosphodiesterase mRNA,<br>complete cds | 1798 1690T>C | C564R |
| U02882 | U02882 | 600129 | GEN-XU  | Human rolipram-sensitive<br>3,5-cyclic AMP<br>phosphodiesterase mRNA,<br>complete cds                                           | 1881 1773G>A | S     |
| U02882 | U02882 | 600129 | GEN-XU  | Human rolipram-sensitive<br>3,5-cyclic AMP<br>phosphodiesterase mRNA,<br>complete cds                                           | 4691 4583T>G | 3     |
| U04735 | U04735 | 601100 | GEN-15A | Human rolipram-sensitive<br>3,5-cyclic AMP<br>phosphodiesterase mRNA,<br>complete cds                                           | 2120 2084A>G | 3     |
| NTRK3  | U05012 | 191316 | GEN-16V | Human microsomal stress<br>70 protein ATPase core<br>(stch) mRNA, complete cds                                                  | 364 209G>A   | S70N  |
| NTRK3  | U05012 | 191316 | GEN-16V | Human receptor tyrosine<br>kinase TrkC (NTRK3)<br>mRNA, complete cds                                                            | 728 573C>T   | S     |
| NTRK3  | U05012 | 191316 | GEN-16V | Human receptor tyrosine<br>kinase TrkC (NTRK3)<br>mRNA, complete cds                                                            | 1613 1458C>T | S     |
| NTRK3  | U05012 | 191316 | GEN-16V | Human receptor tyrosine<br>kinase TrkC (NTRK3)<br>mRNA, complete cds                                                            | 1643 1488G>C | S     |

|      |        |        |         |     |                                                                                                       |             |       |
|------|--------|--------|---------|-----|-------------------------------------------------------------------------------------------------------|-------------|-------|
| DDH1 | U05598 | 600450 | GEN-184 | 16V | kinase TrkC (NTRK3)<br>mRNA, complete cds<br>Human dihydrodiol<br>dehydrogenase mRNA,<br>complete cds | 38 15C>T    | S     |
| DDH1 | U05598 | 600450 | GEN-184 |     | Human dihydrodiol<br>dehydrogenase mRNA,<br>complete cds                                              | 282 259A>T  | S87C  |
| DDH1 | U05598 | 600450 | GEN-184 |     | Human dihydrodiol<br>dehydrogenase mRNA,<br>complete cds                                              | 350 327C>T  | S     |
| DDH1 | U05598 | 600450 | GEN-184 |     | Human dihydrodiol<br>dehydrogenase mRNA,<br>complete cds                                              | 365 342T>C  | S     |
| DDH1 | U05598 | 600450 | GEN-184 |     | Human dihydrodiol<br>dehydrogenase mRNA,<br>complete cds                                              | 464 441G>A  | S     |
| DDH1 | U05598 | 600450 | GEN-184 |     | Human dihydrodiol<br>dehydrogenase mRNA,<br>complete cds                                              | 474 451A>G  | M151V |
| DDH1 | U05598 | 600450 | GEN-184 |     | Human dihydrodiol<br>dehydrogenase mRNA,<br>complete cds                                              | 532 509A>G  | H170R |
| DDH1 | U05598 | 600450 | GEN-184 |     | Human dihydrodiol<br>dehydrogenase mRNA,<br>complete cds                                              | 538 515T>A  | L172Q |
| DDH1 | U05598 | 600450 | GEN-184 |     | Human dihydrodiol<br>dehydrogenase mRNA,<br>complete cds                                              | 689 666T>C  | S     |
| DDH1 | U05598 | 600450 | GEN-184 |     | Human dihydrodiol<br>dehydrogenase mRNA,<br>complete cds                                              | 806 783G>A  | S     |
| DDH1 | U05598 | 600450 | GEN-184 |     | Human dihydrodiol<br>dehydrogenase mRNA,<br>complete cds                                              | 872 849G>T  | S     |
| DDH1 | U05598 | 600450 | GEN-184 |     | Human dihydrodiol<br>dehydrogenase mRNA,<br>complete cds                                              | 952 929T>G  | I310S |
| DDH1 | U05598 | 600450 | GEN-184 |     | Human dihydrodiol<br>dehydrogenase mRNA,<br>complete cds                                              | 1020 997G>A | 3     |

|        |        |        |         |                                                                                         |              |        |
|--------|--------|--------|---------|-----------------------------------------------------------------------------------------|--------------|--------|
| DDH1   | U05598 | 600450 | GEN-184 | Human dihydrodiol dehydrogenase mRNA, complete cds                                      | 1035 1012G>A | 3      |
| DDH1   | U05598 | 600450 | GEN-184 | Human dihydrodiol dehydrogenase mRNA, complete cds                                      | 1112 1089C>T | 3      |
| U05875 | U05875 | 147569 | GEN-18J | Human clone pSK1 interferon gamma receptor accessory factor-1 (AF-1) mRNA, complete cds | 2047 1399C>G | 3      |
| U05875 | U05875 | 147569 | GEN-18J | Human clone pSK1 interferon gamma receptor accessory factor-1 (AF-1) mRNA, complete cds | 2087 1439T>C | 3      |
| U07225 | U07225 | 600041 | GEN-1DM | P2Y2 purinoceptor                                                                       | 2008 1763G>A | 3      |
| U07364 | U07364 | 600504 | GEN-1DS | Inwardly rectifying potassium channel                                                   | 982 885G>A   | S      |
| U07364 | U07364 | 600504 | GEN-1DS | Inwardly rectifying potassium channel                                                   | 1099 1002A>G | S      |
| U07364 | U07364 | 600504 | GEN-1DS | Inwardly rectifying potassium channel                                                   | 1537 1440G>A | 3      |
| U07364 | U07364 | 600504 | GEN-1DS | Inwardly rectifying potassium channel                                                   | 1714 1617G>A | 3      |
| AMPH   | U07616 | 600418 | GEN-1ED | potassium channel                                                                       | 1856 1746G>T | S      |
| AMPH   | U07616 | 600418 | GEN-1ED | Human amphiphysin mRNA, complete cds                                                    | 1901 1791G>A | S      |
| AMPH   | U07616 | 600418 | GEN-1ED | Human amphiphysin mRNA, complete cds                                                    | 2289 2179A>G | 3      |
| U08989 | U08989 | 133550 | GEN-CBZ | Human glutamate transporter mRNA, complete cds                                          | 684 519C>T   | S      |
| U08989 | U08989 | 133550 | GEN-CBZ | Human glutamate transporter mRNA, complete cds                                          | 1617 1452T>C | S      |
| U09002 | U09002 | 138253 | GEN-1G8 | Glutamate Aspartate receptor NMDA 2A                                                    | 1430 1275A>G | S      |
| U09002 | U09002 | 138253 | GEN-1G8 | Glutamate Aspartate receptor NMDA 2A                                                    | 4468 4313T>C | M1438T |
| U09002 | U09002 | 138253 | GEN-1G8 | Glutamate Aspartate receptor NMDA 2A                                                    | 4671 4516G>T | 3      |

|         |        |        |             |                                                                      |               |       |
|---------|--------|--------|-------------|----------------------------------------------------------------------|---------------|-------|
| U09002  | U09002 | 138253 | 1G8<br>GEN- | receptor NMDA 2A                                                     | 5562 5407delC | F     |
| U09002  | U09002 | 138253 | 1G8<br>GEN- | Glutamate Aspartate<br>receptor NMDA 2A                              | 5765 5610C>T  | 3     |
| SLC18A3 | U09210 | 600336 | 1G8<br>GEN- | Glutamate Aspartate<br>receptor NMDA 2A                              | 1369 927A>G   | S     |
| SLC18A3 | U09210 | 600336 | 4F3         | Human vesicular<br>acetylcholine transporter<br>mRNA, complete cds   | 1567 1125C>G  | S     |
| SLC18A3 | U09210 | 600336 | 4F3         | Human vesicular<br>acetylcholine transporter<br>mRNA, complete cds   | 2080 1638G>T  | 3     |
| SLC18A3 | U09210 | 600336 | 4F3         | Human vesicular<br>acetylcholine transporter<br>mRNA, complete cds   | 2199 1757G>A  | 3     |
| SLC18A3 | U09210 | 600336 | 4F3         | Human vesicular<br>acetylcholine transporter<br>mRNA, complete cds   | 2349 1907G>T  | 3     |
| U09806  | U09806 | None   | GEN-<br>4FZ | Human vesicular<br>acetylcholine transporter<br>mRNA, complete cds   | 120 120T>C    | S     |
| U09806  | U09806 | None   | GEN-<br>4FZ | Human<br>methylenetetrahydrofolate<br>reductase mRNA, partial<br>cds | 473 473G>A    | R158Q |
| U09806  | U09806 | None   | GEN-<br>4FZ | Human<br>methylenetetrahydrofolate<br>reductase mRNA, partial<br>cds | 550 550C>T    | F     |
| U09806  | U09806 | None   | GEN-<br>4FZ | Human<br>methylenetetrahydrofolate<br>reductase mRNA, partial<br>cds | 668 668C>T    | A223V |
| U09806  | U09806 | None   | GEN-<br>4FZ | Human<br>methylenetetrahydrofolate<br>reductase mRNA, partial<br>cds | 1059 1059T>C  | S     |
| U09806  | U09806 | None   | GEN-        | Human<br>methylenetetrahydrofolate<br>reductase mRNA, partial<br>cds | 1289 1289C>A  | E430A |

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|        |        |        |         |                                                                             |      |                   |       |
|--------|--------|--------|---------|-----------------------------------------------------------------------------|------|-------------------|-------|
| PDE4A  | U18087 | 600126 | GEN-214 | HPDE4A6 mRNA,<br>complete cds                                               | 1616 | 1607A>C           | E536A |
|        |        |        |         | Human 3,5-cyclic AMP<br>phosphodiesterase<br>HPDE4A6 mRNA,<br>complete cds  |      |                   |       |
| U19251 | U19251 | 600355 | GEN-221 | Homo sapiens neuronal<br>apoptosis inhibitory protein<br>mRNA, complete cds | 2223 | 1932T>G           | F644L |
| U19251 | U19251 | 600355 | GEN-221 | Homo sapiens neuronal<br>apoptosis inhibitory protein<br>mRNA, complete cds | 3046 | 2755C>T           | P919S |
| U19251 | U19251 | 600355 | GEN-221 | Homo sapiens neuronal<br>apoptosis inhibitory protein<br>mRNA, complete cds | 5503 | 5212A>G           | 3     |
| U19251 | U19251 | 600355 | GEN-221 | Homo sapiens neuronal<br>apoptosis inhibitory protein<br>mRNA, complete cds | 5634 | 5343A>G           | 3     |
| U19251 | U19251 | 600355 | GEN-221 | Homo sapiens neuronal<br>apoptosis inhibitory protein<br>mRNA, complete cds | 5644 | 5353A>G           | 3     |
| U19487 | U19487 | 176804 | GEN-41  | PROSTAGLANDIN E2<br>RECEPTOR, EP2<br>SUBTYPE                                | 231  | 75A>T             | S     |
| U19720 | U19720 | 600424 | GEN-I1  | Folate Transporter<br>(SLC19A1)                                             | 53   | (-43)T>C          | 5     |
| U19720 | U19720 | 600424 | GEN-I1  | Folate Transporter<br>(SLC19A1)                                             | 175  | 80G>A             | R27H  |
| U19720 | U19720 | 600424 | GEN-I1  | Folate Transporter<br>(SLC19A1)                                             | 175  | 80G>A             | R27H  |
| U19720 | U19720 | 600424 | GEN-I1  | Folate Transporter<br>(SLC19A1)                                             | 341  | 246C>G            | S     |
| U19720 | U19720 | 600424 | GEN-I1  | Folate Transporter<br>(SLC19A1)                                             | 791  | 696C>T            | S     |
| U19720 | U19720 | 600424 | GEN-I1  | Folate Transporter<br>(SLC19A1)                                             | 1067 | 972G>A            | S     |
| U19720 | U19720 | 600424 | GEN-I1  | Folate Transporter<br>(SLC19A1)                                             | 2100 | 2005*2006ins<br>G | F     |
| U19720 | U19720 | 600424 | GEN-I1  | Folate Transporter<br>(SLC19A1)                                             | 2582 | 2487T>G           | 3     |
| U19720 | U19720 | 600424 | GEN-I1  | Folate Transporter<br>(SLC19A1)                                             | 2582 | 2487T>G           | 3     |

|        |        |        |             |                                                                                                                              |                          |       |
|--------|--------|--------|-------------|------------------------------------------------------------------------------------------------------------------------------|--------------------------|-------|
| U19720 | U19720 | 600424 | GEN-11      | (SLC19A1)<br>Folate Transporter                                                                                              | 2617 2522C>T             | 3     |
| U19720 | U19720 | 600424 | GEN-11      | (SLC19A1)<br>Folate Transporter                                                                                              | 2617 2522C>T             | 3     |
| U19720 | U19720 | 600424 | GEN-11      | (SLC19A1)<br>Folate Transporter                                                                                              | 2652 2557T>C             | 3     |
| U20157 | U20157 | 601690 | GEN-234     | Human platelet-activating<br>factor acetylhydrolase<br>mRNA, complete cds                                                    | 1297 1136T>C             | V379A |
| U23143 | U23143 | 138450 | GEN-<br>MIY | Human mitochondrial<br>serine<br>hydroxymethyltransferase<br>gene, nuclear encoded<br>mitochondrion protein,<br>complete cds | 506 506T>G               | F169C |
| U25029 | U25029 | 138040 | GEN-82      | Glucocorticoid receptor<br>alpha                                                                                             | 335 335C>T               | 3     |
| U25029 | U25029 | 138040 | GEN-82      | Glucocorticoid receptor<br>alpha                                                                                             | 386 386T>C               | 3     |
| U25029 | U25029 | 138040 | GEN-82      | Glucocorticoid receptor<br>alpha                                                                                             | 1069 1069C>T             | 3     |
| U26553 | U26553 | 114131 | GEN-66      | Calcitonin Receptor                                                                                                          | 1412 1340C>T             | P447L |
| U26553 | U26553 | 114131 | GEN-66      | Calcitonin Receptor                                                                                                          | 1515 1443T>C             | 3     |
| U26648 | U26648 | 603189 | GEN-IC      | Syntaxin 5A                                                                                                                  | 501 475C>T               | R159W |
| U26648 | U26648 | 603189 | GEN-IC      | Syntaxin 5A                                                                                                                  | 1270 1244G>A             | 3     |
| U26648 | U26648 | 603189 | GEN-IC      | Syntaxin 5A                                                                                                                  | 1288 1262G>T             | 3     |
| U27699 | U27699 | 603080 | GEN-<br>2C9 | Human pephBGT-1<br>betaine-GABA transporter<br>mRNA, complete cds                                                            | 2841 2255C>T             | 3     |
| U32315 | U32315 | 600876 | GEN-IL      | syntaxin 3                                                                                                                   | 411 373C>T               | R125W |
| U32315 | U32315 | 600876 | GEN-IL      | syntaxin 3                                                                                                                   | 1601 1563G>A             | 3     |
| U32500 | U32500 | 162642 | GEN-1P      | Neuropeptide Y2                                                                                                              | 407 159C>T               | S     |
| U32500 | U32500 | 162642 | GEN-1P      | Neuropeptide Y2                                                                                                              | 833 585T>C               | S     |
| U32500 | U32500 | 162642 | GEN-1P      | Neuropeptide Y2                                                                                                              | 833 585T>C               | S     |
| U32500 | U32500 | 162642 | GEN-1P      | Neuropeptide Y2                                                                                                              | 1184 936T>C              | S     |
| U32500 | U32500 | 162642 | GEN-1P      | Neuropeptide Y2                                                                                                              | 1184 936T>C              | S     |
| U32500 | U32500 | 162642 | GEN-1P      | Neuropeptide Y2                                                                                                              | 1706 1458-<br>1460TAT>TA | 3     |

|        |        |        |         |                                                                     |                          |       |       |
|--------|--------|--------|---------|---------------------------------------------------------------------|--------------------------|-------|-------|
| U32500 | U32500 | 162642 | GEN-1P  | Neuropeptide Y2                                                     | 1706 1458-<br>1460delTAT | T     | 3     |
| U32500 | U32500 | 162642 | GEN-1P  | Neuropeptide Y2                                                     | 2782 2534*2535ins<br>CA  | F     | F     |
| U32989 | U32989 | 191070 | GEN-2JH | Human tryptophan<br>oxygenase (TDO) mRNA,<br>complete cds           | 991 927G>A               | S     | S     |
| U33052 | U33052 | 602549 | GEN-2JL | Human lipid-activated,<br>protein kinase PRK2<br>mRNA, complete cds | 34 25G>C                 | E9Q   | E9Q   |
| U33052 | U33052 | 602549 | GEN-2JL | Human lipid-activated,<br>protein kinase PRK2<br>mRNA, complete cds | 430 421T>C               | S     | S     |
| U33052 | U33052 | 602549 | GEN-2JL | Human lipid-activated,<br>protein kinase PRK2<br>mRNA, complete cds | 1112 1103T>G             | F368C | F368C |
| U33053 | U33053 | 601032 | GEN-2JK | Human lipid-activated<br>protein kinase PRK1<br>mRNA, complete cds  | 656 572A>G               | D191G | D191G |
| U33053 | U33053 | 601032 | GEN-2JK | Human lipid-activated<br>protein kinase PRK1<br>mRNA, complete cds  | 2608 2524G>A             | A842T | A842T |
| U33053 | U33053 | 601032 | GEN-2JK | Human lipid-activated<br>protein kinase PRK1<br>mRNA, complete cds  | 2649 2565G>A             | S     | S     |
| U33053 | U33053 | 601032 | GEN-2JK | Human lipid-activated<br>protein kinase PRK1<br>mRNA, complete cds  | 2713 2629C>T             | S     | S     |
| U33053 | U33053 | 601032 | GEN-2JK | Human lipid-activated<br>protein kinase PRK1<br>mRNA, complete cds  | 2785 2701G>A             | V901I | V901I |
| U33053 | U33053 | 601032 | GEN-2JK | Human lipid-activated<br>protein kinase PRK1<br>mRNA, complete cds  | 2846 2762C>G             | A921G | A921G |
| U33053 | U33053 | 601032 | GEN-2JK | Human lipid-activated<br>protein kinase PRK1<br>mRNA, complete cds  | 2856 2772C>T             | S     | S     |
| U33053 | U33053 | 601032 | GEN-2JK | Human lipid-activated<br>protein kinase PRK1<br>mRNA, complete cds  | 2860 2776G>A             | A926T | A926T |



|        |        |        |         |                                                                         |              |   |
|--------|--------|--------|---------|-------------------------------------------------------------------------|--------------|---|
| U33053 | U33053 | 601032 | GEN-2JK | Human lipid-activated protein kinase PRK1 mRNA, complete cds            | 2889 2805C>T | S |
| U33053 | U33053 | 601032 | GEN-2JK | Human lipid-activated protein kinase PRK1 mRNA, complete cds            | 2895 2811C>T | S |
| U33053 | U33053 | 601032 | GEN-2JK | Human lipid-activated protein kinase PRK1 mRNA, complete cds            | 2954 2870C>T | 3 |
| U33632 | U33632 | 601745 | GEN-IN  | Two P-domain K <sup>+</sup> channel TWIK-1 mRNA                         | 1386 1204G>A | 3 |
| PSEN2  | U34349 | 600759 | GEN-2L2 | Human seven transmembrane domain protein (AD3LP/AD5) mRNA, complete cds | 160 69C>T    | S |
| PSEN2  | U34349 | 600759 | GEN-2L2 | Human seven transmembrane domain protein (AD3LP/AD5) mRNA, complete cds | 220 129C>T   | S |
| PSEN2  | U34349 | 600759 | GEN-2L2 | Human seven transmembrane domain protein (AD3LP/AD5) mRNA, complete cds | 220 129C>T   | S |
| PSEN2  | U34349 | 600759 | GEN-2L2 | Human seven transmembrane domain protein (AD3LP/AD5) mRNA, complete cds | 352 261C>T   | S |
| PSEN2  | U34349 | 600759 | GEN-2L2 | Human seven transmembrane domain protein (AD3LP/AD5) mRNA, complete cds | 352 261C>T   | S |
| PSEN2  | U34349 | 600759 | GEN-2L2 | Human seven transmembrane domain protein (AD3LP/AD5) mRNA, complete cds | 1437 1346C>T | 3 |
| PSEN2  | U34349 | 600759 | GEN-2L2 | Human seven transmembrane domain protein (AD3LP/AD5) mRNA, complete cds | 1654 1563C>G | 3 |
| PPP2R4 | U37352 | 601645 | GEN-2O5 | Human protein phosphatase 2A Balphat                                    | 2084 1996G>A | 3 |

|        |        |        |         |                                                        |              |       |
|--------|--------|--------|---------|--------------------------------------------------------|--------------|-------|
| TAC2   | U37529 | 162320 | GEN-2OH | regulatory subunit mRNA, complete cds                  | 644 499G>A   | 3     |
| TAC2   | U37529 | 162320 | GEN-2OH | Substance P beta-PPT-A                                 | 694 549T>C   | 3     |
| TAC2   | U37529 | 162320 | GEN-2OH | Substance P beta-PPT-A                                 | 799 654A>G   | 3     |
| TAC2   | U37529 | 162320 | GEN-2OH | Substance P beta-PPT-A                                 | 826 681C>T   | 3     |
| U39412 | U39412 | None   | GEN-2Q5 | Homo sapiens alpha SNAP mRNA, complete cds             | 138 71C>T    | S24L  |
| U39412 | U39412 | None   | GEN-2Q5 | Homo sapiens alpha SNAP mRNA, complete cds             | 290 223C>T   | L75F  |
| U39412 | U39412 | None   | GEN-2Q5 | Homo sapiens alpha SNAP mRNA, complete cds             | 473 406G>A   | V136M |
| U39412 | U39412 | None   | GEN-2Q5 | Homo sapiens alpha SNAP mRNA, complete cds             | 651 584C>G   | T195S |
| U40347 | U40347 | 600950 | GEN-2RK | Human serotonin N-acetyltransferase mRNA, complete cds | 382 148G>A   | E50K  |
| U40396 | U40396 | 602691 | GEN-6W  | Steroid receptor coactivator (SRC-1)                   | 285 229A>C   | K77Q  |
| U40396 | U40396 | 602691 | GEN-6W  | Steroid receptor coactivator (SRC-1)                   | 314 258A>T   | K86N  |
| U40396 | U40396 | 602691 | GEN-6W  | Steroid receptor coactivator (SRC-1)                   | 336 280C>T   | P94S  |
| U40396 | U40396 | 602691 | GEN-6W  | Steroid receptor coactivator (SRC-1)                   | 688 632C>T   | T211I |
| U40396 | U40396 | 602691 | GEN-6W  | Steroid receptor coactivator (SRC-1)                   | 970 914C>A   | A305E |
| U40396 | U40396 | 602691 | GEN-6W  | Steroid receptor coactivator (SRC-1)                   | 1511 1455G>A | S     |
| U40396 | U40396 | 602691 | GEN-6W  | Steroid receptor coactivator (SRC-1)                   | 2377 2321C>T | T774M |
| U40396 | U40396 | 602691 | GEN-6W  | Steroid receptor coactivator (SRC-1)                   | 2730 2674C>T | P892S |
| U40583 | U40583 | 118511 | GEN-4O  | Nicotinic, Cholinergic receptor alpha 7                | 661 654T>C   | S     |
| U40583 | U40583 | 118511 | GEN-4O  | Nicotinic, Cholinergic receptor alpha 7                | 697 690A>G   | S     |

|        |        |        |             |                                                       |              |        |
|--------|--------|--------|-------------|-------------------------------------------------------|--------------|--------|
| U40583 | U40583 | 118511 | GEN-4O      | Nicotinic, Cholinergic<br>receptor alpha 7            | 940 933G>A   | S      |
| U40583 | U40583 | 118511 | GEN-4O      | Nicotinic, Cholinergic<br>receptor alpha 7            | 1276 1269T>C | S      |
| U40583 | U40583 | 118511 | GEN-4O      | Nicotinic, Cholinergic<br>receptor alpha 7            | 1790 1783A>T | 3      |
| U40583 | U40583 | 118511 | GEN-4O      | Nicotinic, Cholinergic<br>receptor alpha 7            | 1792 1785T>A | 3      |
| U43030 | U43030 | 600435 | GEN-LFI     | Human cardiotrophin-1<br>(CTF1) mRNA, complete<br>cds | 1404 1372C>T | 3      |
| LEPR   | U43168 | 601007 | GEN-<br>2UN | Human leptin receptor (Ob-<br>r) mRNA, complete cds   | 446 253A>G   | T85A   |
| LEPR   | U43168 | 601007 | GEN-<br>2UN | Human leptin receptor (Ob-<br>r) mRNA, complete cds   | 519 326A>G   | K109R  |
| LEPR   | U43168 | 601007 | GEN-<br>2UN | Human leptin receptor (Ob-<br>r) mRNA, complete cds   | 1222 1029T>C | S      |
| LEPR   | U43168 | 601007 | GEN-<br>2UN | Human leptin receptor (Ob-<br>r) mRNA, complete cds   | 2161 1968G>C | K656N  |
| LEPR   | U43168 | 601007 | GEN-<br>2UN | Human leptin receptor (Ob-<br>r) mRNA, complete cds   | 2174 1981A>C | T661P  |
| LEPR   | U43168 | 601007 | GEN-<br>2UN | Human leptin receptor (Ob-<br>r) mRNA, complete cds   | 3151 2958C>T | S      |
| LEPR   | U43168 | 601007 | GEN-<br>2UN | Human leptin receptor (Ob-<br>r) mRNA, complete cds   | 3250 3057G>A | S      |
| U45448 | U45448 | 600845 | GEN-4FI     | Human P2x1 receptor<br>mRNA, complete cds             | 1424 1228A>G | 3      |
| U45448 | U45448 | 600845 | GEN-4FI     | Human P2x1 receptor<br>mRNA, complete cds             | 1604 1408C>G | 3      |
| U45448 | U45448 | 600845 | GEN-4FI     | Human P2x1 receptor<br>mRNA, complete cds             | 1719 1523G>A | 3      |
| U45448 | U45448 | 600845 | GEN-4FI     | Human P2x1 receptor<br>mRNA, complete cds             | 1827 1631G>A | 3      |
| U45448 | U45448 | 600845 | GEN-4FI     | Human P2x1 receptor<br>mRNA, complete cds             | 2286 2090G>A | 3      |
| U47741 | U47741 | 600140 | GEN-6X      | CREB-binding protein<br>(CBP)                         | 5369 5171A>T | E1724V |
| U47741 | U47741 | 600140 | GEN-6X      | CREB-binding protein<br>(CBP)                         | 5372 5174A>T | D1725V |
| U49516 | U49516 | 312861 | GEN-1Q      | Serotonin 5-HT receptors<br>5-HT2C                    | 2915 2187A>C | 3      |

|        |        |        |         |                                                                                    |              |       |
|--------|--------|--------|---------|------------------------------------------------------------------------------------|--------------|-------|
| U49516 | U49516 | 312861 | GEN-1Q  | Serotonin 5-HT receptors<br>5-HT2C                                                 | 2947 2219A>G | 3     |
| U55206 | U55206 | None   | GEN-35Z | Homo sapiens human<br>gamma-glutamyl hydrolase<br>(hGH) mRNA, complete<br>cds      | 75 16T>C     | C6R   |
| U55206 | U55206 | None   | GEN-35Z | Homo sapiens human<br>gamma-glutamyl hydrolase<br>(hGH) mRNA, complete<br>cds      | 150 91G>A    | A31T  |
| U55206 | U55206 | None   | GEN-35Z | Homo sapiens human<br>gamma-glutamyl hydrolase<br>(hGH) mRNA, complete<br>cds      | 511 452C>T   | T151I |
| U55206 | U55206 | None   | GEN-35Z | Homo sapiens human<br>gamma-glutamyl hydrolase<br>(hGH) mRNA, complete<br>cds      | 1161 1102A>G | 3     |
| U56976 | U56976 | 171891 | GEN-379 | Human calmodulin<br>dependent<br>phosphodiesterase<br>PDE1B1 mRNA, complete<br>cds | 1510 1476C>T | S     |
| U57317 | U57317 | None   | GEN-6Y  | p300/CBP-associated<br>factor (P/CAF)                                              | 2764 2306A>G | D769G |
| CHRNA2 | U62431 | 118502 | GEN-4EN | Nicotinic, Cholinergic<br>receptor alpha 2                                         | 2296 1742C>G | 3     |
| CHRNA2 | U62431 | 118502 | GEN-4EN | Nicotinic, Cholinergic<br>receptor alpha 2                                         | 2387 1833C>T | 3     |
| CHRNA2 | U62431 | 118502 | GEN-4EN | Nicotinic, Cholinergic<br>receptor alpha 2                                         | 2504 1950G>T | 3     |
| CHRNA2 | U62431 | 118502 | GEN-4EN | Nicotinic, Cholinergic<br>receptor alpha 2                                         | 2538 1984G>A | 3     |
| U62433 | U62433 | 118504 | GEN-4P  | Nicotinic, Cholinergic<br>receptor alpha 4                                         | 870 639C>T   | S     |
| U62433 | U62433 | 118504 | GEN-4P  | Nicotinic, Cholinergic<br>receptor alpha 4                                         | 870 639C>T   | S     |
| U62433 | U62433 | 118504 | GEN-4P  | Nicotinic, Cholinergic<br>receptor alpha 4                                         | 909 678C>T   | S     |
| U62433 | U62433 | 118504 | GEN-4P  | Nicotinic, Cholinergic<br>receptor alpha 4                                         | 909 678C>T   | S     |

|        |        |        |         |                                                                                   |              |   |
|--------|--------|--------|---------|-----------------------------------------------------------------------------------|--------------|---|
| U62433 | U62433 | 118504 | GEN-4P  | Nicotinic, Cholinergic receptor alpha 4                                           | 1440 1209T>G | S |
| U62433 | U62433 | 118504 | GEN-4P  | Nicotinic, Cholinergic receptor alpha 4                                           | 1458 1227C>T | S |
| U62433 | U62433 | 118504 | GEN-4P  | Nicotinic, Cholinergic receptor alpha 4                                           | 1860 1629C>T | S |
| U62433 | U62433 | 118504 | GEN-4P  | Nicotinic, Cholinergic receptor alpha 4                                           | 1890 1659G>A | S |
| U62768 | U62768 | 151300 | GEN-3CR | Human oxytocinase splice variant 1 mRNA, complete cds                             | 3356 3295G>C | 3 |
| U62768 | U62768 | 151300 | GEN-3CR | Human oxytocinase splice variant 1 mRNA, complete cds                             | 3547 3486C>T | 3 |
| U71321 | U71321 | 602623 | GEN-2TW | Human FK506-binding protein FKBP51 mRNA, complete cds                             | 1248 1095C>T | S |
| U71321 | U71321 | 602623 | GEN-2TW | Human FK506-binding protein FKBP51 mRNA, complete cds                             | 1425 1272G>A | S |
| U72661 | U72661 | 602062 | GEN-3LK | Human ninjurin1 mRNA, complete cds                                                | 1205 1185C>A | 3 |
| U75283 | U75283 | None   | GEN-3NV | Human sigma receptor mRNA, complete cds                                           | 251 204G>A   | S |
| U75283 | U75283 | None   | GEN-3NV | Human sigma receptor mRNA, complete cds                                           | 1625 1578A>C | 3 |
| U81375 | U81375 | 602193 | GEN-3VO | Human placental equilibrative nucleoside transporter 1 (hENT1) mRNA, complete cds | 1989 1811G>A | 3 |
| U81375 | U81375 | 602193 | GEN-3VO | Human placental equilibrative nucleoside transporter 1 (hENT1) mRNA, complete cds | 1996 1818C>T | 3 |
| U81375 | U81375 | 602193 | GEN-3VO | Human placental equilibrative nucleoside transporter 1 (hENT1) mRNA, complete cds | 2045 1867T>C | 3 |
| U81504 | U81504 | 603401 | GEN-3VX | Homo sapiens beta-3A-adaptin subunit of the AP-3 complex mRNA, complete           | 1775 1683C>T | S |

|        |        |        |         |                                                                             |              |       |
|--------|--------|--------|---------|-----------------------------------------------------------------------------|--------------|-------|
| U81504 | U81504 | 603401 | GEN-3VX | Homo sapiens beta-3A-adaptin subunit of the AP-3 complex mRNA, complete cds | 2108 2016T>C | S     |
| U81504 | U81504 | 603401 | GEN-3VX | Homo sapiens beta-3A-adaptin subunit of the AP-3 complex mRNA, complete cds | 2668 2576G>T | S859I |
| U81554 | U81554 | 602122 | GEN-3VW | Homo sapiens CaM kinase II isoform mRNA, complete cds                       | 939 727A>G   | 3     |
| U84404 | U84404 | 601623 | GEN-83  | Ubiquitin protein ligase E3A                                                | 1003 417A>T  | S     |
| U84404 | U84404 | 601623 | GEN-83  | Ubiquitin protein ligase E3A                                                | 1386 800T>G  | V267G |
| U84404 | U84404 | 601623 | GEN-83  | Ubiquitin protein ligase E3A                                                | 1930 1344A>G | S     |
| U84404 | U84404 | 601623 | GEN-83  | Ubiquitin protein ligase E3A                                                | 2299 1713A>G | S     |
| U95025 | U95025 | 601116 | GEN-4FX | Homo sapiens metabotropic glutamate receptor 8 (GRM8) mRNA, complete cds    | 744 744T>C   | S     |
| U97669 | U97669 | 600276 | GEN-4BU | Homo sapiens Notch3 (NOTCH3) mRNA, complete cds                             | 7712 7634T>G | 3     |
| U97669 | U97669 | 600276 | GEN-4BU | Homo sapiens Notch3 (NOTCH3) mRNA, complete cds                             | 7852 7774A>G | 3     |
| U97669 | U97669 | 600276 | GEN-4BU | Homo sapiens Notch3 (NOTCH3) mRNA, complete cds                             | 7881 7803G>A | 3     |
| U97669 | U97669 | 600276 | GEN-4BU | Homo sapiens Notch3 (NOTCH3) mRNA, complete cds                             | 7934 7856T>C | 3     |
| V00518 | V00518 | 118850 | GEN-P4  | Human messenger RNA for chorionic gonadotropin                              | 565 515T>C   | 3     |
| V00519 | V00519 | 139250 | GEN-4U  | Growth hormone 1                                                            | 299 259C>A   | P87T  |
| V00519 | V00519 | 139250 | GEN-4U  | Growth hormone 1                                                            | 524 484G>T   | G162W |
| IFNB1  | V00546 | 147640 | GEN-TV  | Messenger RNA for human                                                     | 474 410T>G   | L137R |

|        |        |        |         |                                                              |      |          |       |
|--------|--------|--------|---------|--------------------------------------------------------------|------|----------|-------|
| V00548 | V00548 | 147562 | GEN-P2  | fibroblast interferon                                        | 119  | 119G>A   | R40K  |
|        |        |        |         | Human messenger RNA for leukocyte (alpha-2) interferon       |      |          |       |
| V00566 | V00566 | 176760 | GEN-4V  | Prolactin                                                    | 574  | 570G>A   | S     |
| V00571 | V00571 | 122560 | GEN-CBO | corticotropin releasing factor                               | 822  | 637delA  | F     |
| V00571 | V00571 | 122560 | GEN-CBO | corticotropin releasing factor                               | 837  | 652G>A   | 3     |
| X00734 | X00734 | None   | GEN-MST | Human beta-tubulin gene (5-beta) with ten Alu family members | 1059 | 1059G>T  | S     |
| X01394 | X01394 | 191160 | GEN-4Y  | Tumor necrosis factor                                        | 125  | (-28)C>T | 5     |
| X02317 | X02317 | 147450 | GEN-KM  | Superoxide dismutase 1 (Cu/Zn)                               | 614  | 550A>C   | 3     |
| X02415 | X02415 | 134850 | GEN-MJO | Human gene for fibrinogen gamma chain                        | 1000 | 949G>A   | D317N |
| X02812 | X02812 | 190180 | GEN-XR  | Human mRNA for transforming growth factor-beta (TGF-beta)    | 870  | 29C>T    | P10L  |
| X02812 | X02812 | 190180 | GEN-XR  | Human mRNA for transforming growth factor-beta (TGF-beta)    | 979  | 138C>G   | I46M  |
| X02812 | X02812 | 190180 | GEN-XR  | Human mRNA for transforming growth factor-beta (TGF-beta)    | 1632 | 791C>T   | T264I |
| X02812 | X02812 | 190180 | GEN-XR  | Human mRNA for transforming growth factor-beta (TGF-beta)    | 1807 | 966C>T   | S     |
| X02812 | X02812 | 190180 | GEN-XR  | Human mRNA for transforming growth factor-beta (TGF-beta)    | 1930 | 1089G>A  | S     |
| X02812 | X02812 | 190180 | GEN-XR  | Human mRNA for transforming growth factor-beta (TGF-beta)    | 1942 | 1101C>T  | S     |
| X02812 | X02812 | 190180 | GEN-XR  | Human mRNA for transforming growth factor-beta (TGF-beta)    | 2013 | 1172G>A  | S391N |
| X03172 | X03172 | 192340 | GEN-ZM  | Human mRNA for vasopressin precursor                         | 379  | 356T>G   | V119G |
| X03635 | X03635 | 133430 | GEN-50  | estrogen receptors                                           | 390  | 30T>C    | S     |

|        |        |        |         |                                                 |                          |       |
|--------|--------|--------|---------|-------------------------------------------------|--------------------------|-------|
| X03635 | X03635 | 133430 | GEN-50  | estrogen receptors                              | 390 30T>C                | S     |
| X03635 | X03635 | 133430 | GEN-50  | estrogen receptors                              | 424 64G>C                | E22Q  |
| X03635 | X03635 | 133430 | GEN-50  | estrogen receptors                              | 617 257C>T               | A86V  |
| X03635 | X03635 | 133430 | GEN-50  | estrogen receptors                              | 621 261G>C               | S     |
| X03635 | X03635 | 133430 | GEN-50  | estrogen receptors                              | 829 469C>T               | F     |
| X03635 | X03635 | 133430 | GEN-50  | estrogen receptors                              | 1335 975C>G              | S     |
| X03635 | X03635 | 133430 | GEN-50  | estrogen receptors                              | 1335 975C>G              | S     |
| X03635 | X03635 | 133430 | GEN-50  | estrogen receptors                              | 1451 1091T>A             | V364E |
| X03635 | X03635 | 133430 | GEN-50  | estrogen receptors                              | 1674 1314G>A             | M438I |
| X03635 | X03635 | 133430 | GEN-50  | estrogen receptors                              | 2142 1782A>G             | S     |
| X03635 | X03635 | 133430 | GEN-50  | estrogen receptors                              | 2354 1994A>G             | 3     |
| X03635 | X03635 | 133430 | GEN-50  | estrogen receptors                              | 2550 2190A>C             | 3     |
| X03635 | X03635 | 133430 | GEN-50  | estrogen receptors                              | 2733 2373C>G             | 3     |
| X03635 | X03635 | 133430 | GEN-50  | estrogen receptors                              | 3181 2821T>C             | 3     |
| X03635 | X03635 | 133430 | GEN-50  | estrogen receptors                              | 3338 2978C>T             | 3     |
| X03635 | X03635 | 133430 | GEN-50  | estrogen receptors                              | 3652 3292-<br>3294CCT>CC | 3     |
| X03635 | X03635 | 133430 | GEN-50  | estrogen receptors                              | 3652 3292-<br>3294delCCT | 3     |
| X03635 | X03635 | 133430 | GEN-50  | estrogen receptors                              | 3896 3536C>A             | 3     |
| X03635 | X03635 | 133430 | GEN-50  | estrogen receptors                              | 4378 4018T>C             | 3     |
| X03635 | X03635 | 133430 | GEN-50  | estrogen receptors                              | 6287 5927T>C             | 3     |
| X04741 | X04741 | 191342 | GEN-KU  | UBIQUITIN CARBOXYL-<br>TERMINAL HYDROLASE       | 51 20C>A                 | S7Y   |
| X04741 | X04741 | 191342 | GEN-KU  | UBIQUITIN CARBOXYL-<br>TERMINAL HYDROLASE       | 291 260C>G               | A87G  |
| X04741 | X04741 | 191342 | GEN-KU  | UBIQUITIN CARBOXYL-<br>TERMINAL HYDROLASE       | 296 265G>C               | A89P  |
| CST3   | X05607 | 105150 | GEN-189 | Human mRNA for cysteine<br>proteinase inhibitor | 62 (-13)C>G              | 5     |
| CST3   | X05607 | 105150 | GEN-189 | Human mRNA for cysteine<br>proteinase inhibitor | 455 381C>T               | S     |



|        |        |        |         |                                                                 |              |       |
|--------|--------|--------|---------|-----------------------------------------------------------------|--------------|-------|
| CST3   | X05607 | 105150 | GEN-189 | Human mRNA for cysteine<br>proteinase inhibitor                 | 550 476C>T   | 3     |
| CST3   | X05607 | 105150 | GEN-189 | precursor cystatin C                                            | 632 558A>C   | 3     |
| CST3   | X05607 | 105150 | GEN-189 | Human mRNA for cysteine<br>proteinase inhibitor                 | 647 573G>A   | 3     |
| CST3   | X05607 | 105150 | GEN-189 | precursor cystatin C                                            | 713 639C>T   | 3     |
| CST3   | X05607 | 105150 | GEN-189 | Human mRNA for cysteine<br>proteinase inhibitor                 | 746 672A>C   | 3     |
| X06318 | X06318 | 176970 | GEN-KY  | precursor cystatin C                                            | 83 (-54)G>C  | 5     |
| X06318 | X06318 | 176970 | GEN-KY  | Protein kinase C, beta 1                                        | 940 804G>A   | S     |
| X06318 | X06318 | 176970 | GEN-KY  | Protein kinase C, beta 1                                        | 1327 1191T>C | S     |
| X06318 | X06318 | 176970 | GEN-KY  | Protein kinase C, beta 1                                        | 1906 1770C>T | S     |
| X06562 | X06562 | 600946 | GEN-6D  | Growth hormone receptor                                         | 3392 3349A>T | 3     |
| X06562 | X06562 | 600946 | GEN-6D  | Growth hormone receptor                                         | 4145 4102G>A | 3     |
| X07674 | X07674 | 138130 | GEN-1EC | Human mRNA for<br>glutamate dehydrogenase<br>(EC 1.4.1.3., GDH) | 266 253C>T   | S     |
| X07674 | X07674 | 138130 | GEN-1EC | Human mRNA for<br>glutamate dehydrogenase<br>(EC 1.4.1.3., GDH) | 272 259G>A   | E87K  |
| X07674 | X07674 | 138130 | GEN-1EC | Human mRNA for<br>glutamate dehydrogenase<br>(EC 1.4.1.3., GDH) | 288 275G>A   | R92Q  |
| X07674 | X07674 | 138130 | GEN-1EC | Human mRNA for<br>glutamate dehydrogenase<br>(EC 1.4.1.3., GDH) | 292 279G>A   | S     |
| X07674 | X07674 | 138130 | GEN-1EC | Human mRNA for<br>glutamate dehydrogenase<br>(EC 1.4.1.3., GDH) | 595 582T>C   | S     |
| X07674 | X07674 | 138130 | GEN-1EC | Human mRNA for<br>glutamate dehydrogenase<br>(EC 1.4.1.3., GDH) | 598 585T>A   | D195E |
| X07674 | X07674 | 138130 | GEN-1EC | Human mRNA for<br>glutamate dehydrogenase<br>(EC 1.4.1.3., GDH) | 646 633A>G   | S     |

|        |        |        |        |         |                                                                                                               |              |       |
|--------|--------|--------|--------|---------|---------------------------------------------------------------------------------------------------------------|--------------|-------|
| X07674 | X07674 | X07674 | 138130 | GEN-1EC | glutamate dehydrogenase<br>(EC 1.4.1.3., GDH)<br>Human mRNA for glutamate dehydrogenase<br>(EC 1.4.1.3., GDH) | 668 655A>G   | I219V |
| X07674 | X07674 | X07674 | 138130 | GEN-1EC | glutamate dehydrogenase<br>(EC 1.4.1.3., GDH)<br>Human mRNA for glutamate dehydrogenase<br>(EC 1.4.1.3., GDH) | 693 680G>A   | S227N |
| X07674 | X07674 | X07674 | 138130 | GEN-1EC | glutamate dehydrogenase<br>(EC 1.4.1.3., GDH)<br>Human mRNA for glutamate dehydrogenase<br>(EC 1.4.1.3., GDH) | 721 708C>T   | S     |
| X07674 | X07674 | X07674 | 138130 | GEN-1EC | glutamate dehydrogenase<br>(EC 1.4.1.3., GDH)<br>Human mRNA for glutamate dehydrogenase<br>(EC 1.4.1.3., GDH) | 859 846T>C   | S     |
| X07674 | X07674 | X07674 | 138130 | GEN-1EC | glutamate dehydrogenase<br>(EC 1.4.1.3., GDH)<br>Human mRNA for glutamate dehydrogenase<br>(EC 1.4.1.3., GDH) | 1134 1121C>T | A374V |
| X07674 | X07674 | X07674 | 138130 | GEN-1EC | glutamate dehydrogenase<br>(EC 1.4.1.3., GDH)<br>Human mRNA for glutamate dehydrogenase<br>(EC 1.4.1.3., GDH) | 1164 1151G>C | S384T |
| X07674 | X07674 | X07674 | 138130 | GEN-1EC | glutamate dehydrogenase<br>(EC 1.4.1.3., GDH)<br>Human mRNA for glutamate dehydrogenase<br>(EC 1.4.1.3., GDH) | 1255 1242C>T | S     |
| X07674 | X07674 | X07674 | 138130 | GEN-1EC | glutamate dehydrogenase<br>(EC 1.4.1.3., GDH)<br>Human mRNA for glutamate dehydrogenase<br>(EC 1.4.1.3., GDH) | 1415 1402A>C | M468L |
| X07674 | X07674 | X07674 | 138130 | GEN-1EC | glutamate dehydrogenase<br>(EC 1.4.1.3., GDH)<br>Human mRNA for glutamate dehydrogenase<br>(EC 1.4.1.3., GDH) | 1427 1414G>T | F     |
| X07674 | X07674 | X07674 | 138130 | GEN-1EC | glutamate dehydrogenase<br>(EC 1.4.1.3., GDH)<br>Human mRNA for glutamate dehydrogenase<br>(EC 1.4.1.3., GDH) | 1501 1488G>T | R496S |
| X07674 | X07674 | X07674 | 138130 | GEN-1EC | glutamate dehydrogenase<br>(EC 1.4.1.3., GDH)<br>Human mRNA for glutamate dehydrogenase<br>(EC 1.4.1.3., GDH) | 1528 1515C>T | S     |
| X07674 | X07674 | X07674 | 138130 | GEN-1EC | glutamate dehydrogenase<br>(EC 1.4.1.3., GDH)<br>Human mRNA for glutamate dehydrogenase<br>(EC 1.4.1.3., GDH) | 1539 1526G>C | G509A |
| X07674 | X07674 | X07674 | 138130 | GEN-1EC | glutamate dehydrogenase<br>(EC 1.4.1.3., GDH)<br>Human mRNA for glutamate dehydrogenase<br>(EC 1.4.1.3., GDH) | 1581 1568G>A | R523H |

|        |        |        |         |                                                             |              |       |
|--------|--------|--------|---------|-------------------------------------------------------------|--------------|-------|
| X07674 | X07674 | 138130 | GEN-1EC | Human mRNA for glutamate dehydrogenase (EC 1.4.1.3., GDH)   | 1633 1620T>C | S     |
| X07674 | X07674 | 138130 | GEN-1EC | Human mRNA for glutamate dehydrogenase (EC 1.4.1.3., GDH)   | 1645 1632G>A | S     |
| X07674 | X07674 | 138130 | GEN-1EC | Human mRNA for glutamate dehydrogenase (EC 1.4.1.3., GDH)   | 1665 1652A>G | N551S |
| X07674 | X07674 | 138130 | GEN-1EC | Human mRNA for glutamate dehydrogenase (EC 1.4.1.3., GDH)   | 1717 1704T>A | 3     |
| X07674 | X07674 | 138130 | GEN-1EC | Human mRNA for glutamate dehydrogenase (EC 1.4.1.3., GDH)   | 1830 1817G>A | 3     |
| SOD2   | X07834 | 147460 | GEN-1ES | Human mRNA for manganese superoxide dismutase (EC 1.15.1.1) | 44 40C>G     | P14A  |
| SOD2   | X07834 | 147460 | GEN-1ES | Human mRNA for manganese superoxide dismutase (EC 1.15.1.1) | 51 47T>C     | V16A  |
| SOD2   | X07834 | 147460 | GEN-1ES | Human mRNA for manganese superoxide dismutase (EC 1.15.1.1) | 198 194C>A   | T65N  |
| SOD2   | X07834 | 147460 | GEN-1ES | Human mRNA for manganese superoxide dismutase (EC 1.15.1.1) | 249 245T>C   | I82T  |
| X12953 | X12953 | 179509 | GEN-1NA | Human mRNA for related and member of ras family             | 723 515A>C   | Q172P |
| X13561 | X13561 | 147910 | GEN-1OH | Human mRNA for preprokallikrein (EC 3.4.21)                 | 54 18G>T     | S     |
| X13561 | X13561 | 147910 | GEN-1OH | Human mRNA for preprokallikrein (EC 3.4.21)                 | 441 405T>C   | S     |
| X13561 | X13561 | 147910 | GEN-1OH | Human mRNA for preprokallikrein (EC 3.4.21)                 | 469 433G>C   | E145Q |
| X13561 | X13561 | 147910 | GEN-1OH | Human mRNA for preprokallikrein (EC 3.4.21)                 | 592 556A>G   | K186E |
| X13589 | X13589 | 107910 | GEN-56  | Cytochrome P450, subfamily XIX (aromatization of            | 364 240A>G   | S     |

|        |        |        |         |                                                                                    |                           |       |
|--------|--------|--------|---------|------------------------------------------------------------------------------------|---------------------------|-------|
| X13589 | X13589 | 107910 | GEN-56  | androgens)<br>Cytochrome P450,<br>subfamily XIX<br>(aromatization of<br>androgens) | 914 790C>T                | R264C |
| X13589 | X13589 | 107910 | GEN-56  | Cytochrome P450,<br>subfamily XIX<br>(aromatization of<br>androgens)               | 914 790C>T                | R264C |
| X13589 | X13589 | 107910 | GEN-56  | androgens)<br>Cytochrome P450,<br>subfamily XIX<br>(aromatization of<br>androgens) | 1655 1531C>T              | 3     |
| X13589 | X13589 | 107910 | GEN-56  | androgens)<br>Cytochrome P450,<br>subfamily XIX<br>(aromatization of<br>androgens) | 1796 1672G>T              | 3     |
| X13629 | X13629 | 107690 | GEN-100 | Human intestinal mRNA for<br>apolipoprotein A-IV                                   | 881 836G>A                | R279K |
| X13629 | X13629 | 107690 | GEN-100 | Human intestinal mRNA for<br>apolipoprotein A-IV                                   | 1185 1140G>T              | Q380H |
| X13629 | X13629 | 107690 | GEN-100 | Human intestinal mRNA for<br>apolipoprotein A-IV                                   | 1302 1257*1258ins<br>CTGT | F     |
| X13916 | X13916 | 107770 | GEN-1Q1 | Human mRNA for LDL-<br>receptor related protein                                    | 2805 2339C>T              | T780I |
| X13916 | X13916 | 107770 | GEN-1Q1 | Human mRNA for LDL-<br>receptor related protein                                    | 8608 8142G>A              | S     |
| X13916 | X13916 | 107770 | GEN-1Q1 | Human mRNA for LDL-<br>receptor related protein                                    | 8923 8457C>T              | S     |
| X13916 | X13916 | 107770 | GEN-1Q1 | Human mRNA for LDL-<br>receptor related protein                                    | 9034 8568G>T              | S     |
| X13916 | X13916 | 107770 | GEN-1Q1 | Human mRNA for LDL-<br>receptor related protein                                    | 9040 8574C>T              | S     |
| X13916 | X13916 | 107770 | GEN-1Q1 | Human mRNA for LDL-<br>receptor related protein                                    | 9391 8925T>C              | S     |
| LIF    | X13967 | 159540 | GEN-1PZ | Human mRNA for<br>leukaemia inhibitory factor<br>(LIF/HILDA)                       | 3710 3666T>G              | 3     |
| CLU    | X14723 | 185430 | GEN-1SB | Human SP-40,40 mRNA<br>for complement-associated<br>protein SP-40,40 alpha-1       | 131 84C>T                 | S     |

|        |        |        |         |                                                                                         |              |       |
|--------|--------|--------|---------|-----------------------------------------------------------------------------------------|--------------|-------|
| CLU    | X14723 | 185430 | GEN-1SB | Human SP-40,40 mRNA for complement-associated protein SP-40,40 alpha-1 and beta-1 chain | 429 382G>T   | V128F |
| CLU    | X14723 | 185430 | GEN-1SB | Human SP-40,40 mRNA for complement-associated protein SP-40,40 alpha-1 and beta-1 chain | 836 789C>T   | S     |
| CLU    | X14723 | 185430 | GEN-1SB | Human SP-40,40 mRNA for complement-associated protein SP-40,40 alpha-1 and beta-1 chain | 1234 1187C>T | S396L |
| CLU    | X14723 | 185430 | GEN-1SB | Human SP-40,40 mRNA for complement-associated protein SP-40,40 alpha-1 and beta-1 chain | 1372 1325A>T | Y442F |
| CLU    | X14723 | 185430 | GEN-1SB | Human SP-40,40 mRNA for complement-associated protein SP-40,40 alpha-1 and beta-1 chain | 1482 1435C>T | 3     |
| CLU    | X14723 | 185430 | GEN-1SB | Human SP-40,40 mRNA for complement-associated protein SP-40,40 alpha-1 and beta-1 chain | 1548 1501C>T | 3     |
| CLU    | X14723 | 185430 | GEN-1SB | Human SP-40,40 mRNA for complement-associated protein SP-40,40 alpha-1 and beta-1 chain | 1645 1598A>T | 3     |
| X14766 | X14766 | 137160 | GEN-1X  | Gamma-aminobutyric acid (GABA) A receptor                                               | 370 156C>T   | S     |
| CHRN1  | X14830 | 100710 | GEN-4EK | Nicotinic, Cholinergic receptor beta 1                                                  | 1375 1359C>T | S     |
| CHRN1  | X14830 | 100710 | GEN-4EK | Nicotinic, Cholinergic receptor beta 1                                                  | 1591 1575T>C | 3     |
| X15263 | X15263 | None   | GEN-4EQ | Muscarinic receptor, CHRM1                                                              | 1144 1044G>A | S     |
| X15357 | X15357 | 108960 | GEN-KUV | Human mRNA for natriuretic peptide receptor (ANP-A receptor)                            | 1066 1023G>C | M341I |
| X15357 | X15357 | 108960 | GEN-    | Human mRNA for                                                                          | 1657 1614C>T | S     |

|        |        |        |         |                                                              |                        |       |
|--------|--------|--------|---------|--------------------------------------------------------------|------------------------|-------|
| X15357 | X15357 | 108960 | KUV     | natriuretic peptide receptor (ANP-A receptor)                | 2859 2816G>A           | R939Q |
| X15357 | X15357 | 108960 | GEN-KUV | Human mRNA for natriuretic peptide receptor (ANP-A receptor) | 2983 2940G>A           | S     |
| X15357 | X15357 | 108960 | GEN-KUV | Human mRNA for natriuretic peptide receptor (ANP-A receptor) | 3259 3216delC          | F     |
| X15357 | X15357 | 108960 | GEN-KUV | Human mRNA for natriuretic peptide receptor (ANP-A receptor) | 3589 3546*3547ins GAAA | F     |
| X16087 | X16087 | 272750 | GEN-1XG | Human mRNA for G(M2) activator protein                       | 13 13A>G               | T5A   |
| X16087 | X16087 | 272750 | GEN-1XG | Human mRNA for G(M2) activator protein                       | 133 133G>A             | V45I  |
| X16087 | X16087 | 272750 | GEN-1XG | Human mRNA for G(M2) activator protein                       | 163 163G>A             | V55M  |
| PACE   | X17094 | 136950 | GEN-1ZV | Human fur mRNA for furin                                     | 399 183C>T             | S     |
| PACE   | X17094 | 136950 | GEN-1ZV | Human fur mRNA for furin                                     | 1692 1476C>T           | S     |
| PACE   | X17094 | 136950 | GEN-1ZV | Human fur mRNA for furin                                     | 2067 1851C>G           | S     |
| PACE   | X17094 | 136950 | GEN-1ZV | Human fur mRNA for furin                                     | 2725 2509T>C           | 3     |
| PACE   | X17094 | 136950 | GEN-1ZV | Human fur mRNA for furin                                     | 2855 2639C>A           | 3     |
| PACE   | X17094 | 136950 | GEN-1ZV | Human fur mRNA for furin                                     | 2988 2772G>A           | 3     |
| PACE   | X17094 | 136950 | GEN-1ZV | Human fur mRNA for furin                                     | 3234 3018C>T           | 3     |
| PACE   | X17094 | 136950 | GEN-1ZV | Human fur mRNA for furin                                     | 3625 3409A>G           | 3     |
| PACE   | X17094 | 136950 | GEN-1ZV | Human fur mRNA for furin                                     | 3883 3667C>T           | 3     |
| PACE   | X17094 | 136950 | GEN-1ZV | Human fur mRNA for furin                                     | 4053 3837A>G           | 3     |
| X51362 | X51362 | 126450 | GEN-    | Dopamine Receptor D2                                         | 588 423G>A             | S     |

|        |        |        |               |                                                                                           |              |       |
|--------|--------|--------|---------------|-------------------------------------------------------------------------------------------|--------------|-------|
| X51362 | X51362 | 126450 | 31W<br>GEN-   | Dopamine Receptor D2                                                                      | 1104 939C>T  | S     |
| X51362 | X51362 | 126450 | 31W<br>GEN-   | Dopamine Receptor D2                                                                      | 1122 957T>C  | S     |
| X51362 | X51362 | 126450 | 31W<br>GEN-   | Dopamine Receptor D2                                                                      | 1248 1083A>G | S     |
| X51362 | X51362 | 126450 | 31W<br>GEN-   | Dopamine Receptor D2                                                                      | 1488 1323T>C | S     |
| X51362 | X51362 | 126450 | 31W<br>GEN-   | Dopamine Receptor D2                                                                      | 1548 1383A>G | 3     |
| X51362 | X51362 | 126450 | 31W<br>GEN-   | Dopamine Receptor D2                                                                      | 2361 2196C>T | 3     |
| X51416 | X51416 | 601998 | 31W<br>GEN-57 | STEROID HORMONE<br>RECEPTOR ERR1                                                          | 2285 2222G>A | 3     |
| FGFR1  | X51803 | 136350 | GEN-<br>32G   | Human mRNA for<br>fibroblast growth factor<br>(FGF) receptor                              | 276 159T>G   | S     |
| EDN3   | X52001 | 131242 | GEN-<br>33E   | Endothelin 3                                                                              | 1262 1152G>A | 3     |
| EDN3   | X52001 | 131242 | GEN-<br>33E   | Endothelin 3                                                                              | 1649 1539C>G | 3     |
| EDN3   | X52001 | 131242 | GEN-<br>33E   | Endothelin 3                                                                              | 1700 1590C>T | 3     |
| EDN3   | X52001 | 131242 | GEN-<br>33E   | Endothelin 3                                                                              | 1742 1632C>T | 3     |
| EDN3   | X52001 | 131242 | GEN-<br>33E   | Endothelin 3                                                                              | 1797 1687C>T | 3     |
| EDN3   | X52001 | 131242 | GEN-<br>33E   | Endothelin 3                                                                              | 1914 1804G>C | 3     |
| EDN3   | X52001 | 131242 | GEN-<br>33E   | Endothelin 3                                                                              | 2040 1930C>T | 3     |
| X52008 | X52008 | 305990 | GEN-22        | Glycine receptor alpha2                                                                   | 591 204T>G   | S     |
| GLRA1  | X52009 | 138491 | GEN-4FJ       | H.sapiens alpha-1<br>strychnine binding subunit<br>of inhibitory glycine<br>receptor mRNA | 1477 1181C>T | P394L |
| GLRA1  | X52009 | 138491 | GEN-4FJ       | H.sapiens alpha-1<br>strychnine binding subunit<br>of inhibitory glycine<br>receptor mRNA | 1520 1224C>T | S     |

|        |        |        |         |                                                                                                                            |              |       |
|--------|--------|--------|---------|----------------------------------------------------------------------------------------------------------------------------|--------------|-------|
| X52479 | X52479 | 176960 | GEN-LM  | Protein kinase C, alpha                                                                                                    | 908 881A>C   | D294A |
| NGFB   | X52599 | 162030 | GEN-33V | Human mRNA for beta nerve growth factor                                                                                    | 832 663G>A   | S     |
| PDHA1  | X52709 | 312170 | GEN-33Y | Human mRNA for brain pyruvate dehydrogenase (EC 1.2.4.1)                                                                   | 849 795A>G   | S     |
| PDHA1  | X52709 | 312170 | GEN-33Y | Human mRNA for brain pyruvate dehydrogenase (EC 1.2.4.1)                                                                   | 1337 1283C>T | 3     |
| PDHA1  | X52709 | 312170 | GEN-33Y | Human mRNA for brain pyruvate dehydrogenase (EC 1.2.4.1)                                                                   | 1416 1362G>A | 3     |
| X52773 | X52773 | 180245 | GEN-74  | Retinoid X receptor, alpha                                                                                                 | 1744 1669G>A | 3     |
| FGFR2  | X52832 | 176943 | GEN-341 | Human bek mRNA for fibroblast growth factor receptor-BEK                                                                   | 338 159A>G   | S     |
| FGFR2  | X52832 | 176943 | GEN-341 | Human bek mRNA for fibroblast growth factor receptor-BEK                                                                   | 2903 2724A>T | 3     |
| CHRNA3 | X53559 | 118503 | GEN-34I | Nicotinic, Cholinergic receptor alpha 3                                                                                    | 212 212A>G   | D71G  |
| CHRNA3 | X53559 | 118503 | GEN-34I | Nicotinic, Cholinergic receptor alpha 3                                                                                    | 552 552C>T   | S     |
| X54199 | X54199 | 138440 | GEN-LS  | Phosphoribosylglycinamide formyltransferase, phosphoribosylglycinamide synthetase, phosphoribosylaminoimidazole synthetase | 168 90G>A    | S     |
| X54315 | X54315 | 114020 | GEN-351 | Human mRNA for N-cadherin                                                                                                  | 2549 2448T>C | S     |
| AGXT   | X56092 | 259900 | GEN-36R | Human Ser-PyrAT mRNA for serine-pyruvate aminotransferase                                                                  | 1234 1213C>A | 3     |
| FGFR4  | X57205 | 134935 | GEN-37M | Human FGFR-4 mRNA for fibroblast growth factor receptor (FGFR-4)                                                           | 83 28G>A     | V10I  |
| FGFR4  | X57205 | 134935 | GEN-37M | Human FGFR-4 mRNA for fibroblast growth factor receptor (FGFR-4)                                                           | 217 162T>G   | S     |
| YWHAB  | X57346 | 601289 | GEN-    | H.sapiens mRNA for HS1                                                                                                     | 432 60C>A    | S     |



|        |        |        |         |                                                                              |              |       |
|--------|--------|--------|---------|------------------------------------------------------------------------------|--------------|-------|
| YWHAB  | X57346 | 601289 | GEN-37R | H.sapiens mRNA for HS1 protein                                               | 1135 763T>C  | 3     |
| X57348 | X57348 | 601290 | GEN-37R | H.sapiens mRNA (clone 9112)                                                  | 1317 1152C>T | 3     |
| X57348 | X57348 | 601290 | GEN-37S | H.sapiens mRNA (clone 9112)                                                  | 1342 1177C>T | 3     |
| X57830 | X57830 | 182135 | GEN-37S | Serotonin 5-HT2 receptor                                                     | 247 102T>C   | S     |
| CRHBP  | X58022 | 122559 | GEN-38K | Human mRNA for corticotropin-releasing factor binding protein (CRF-BP)       | 987 941T>G   | I314S |
| DRD1   | X58987 | 126449 | GEN-4EH | D1 dopaminergic receptor                                                     | 229 (-48)A>G | 5     |
| DRD1   | X58987 | 126449 | GEN-4EH | D1 dopaminergic receptor                                                     | 366 90G>A    | S     |
| DRD1   | X58987 | 126449 | GEN-4EH | D1 dopaminergic receptor                                                     | 474 198G>A   | S     |
| DRD1   | X58987 | 126449 | GEN-4EH | D1 dopaminergic receptor                                                     | 1539 1263G>A | S     |
| X59834 | X59834 | 138290 | GEN-M4  | Glutamate-ammonia ligase (glutamine synthase)                                | 67 (-43)G>C  | 5     |
| X59834 | X59834 | 138290 | GEN-M4  | Glutamate-ammonia ligase (glutamine synthase)                                | 304 195T>C   | S     |
| X59834 | X59834 | 138290 | GEN-M4  | Glutamate-ammonia ligase (glutamine synthase)                                | 1127 1018C>T | R340C |
| X59834 | X59834 | 138290 | GEN-M4  | Glutamate-ammonia ligase (glutamine synthase)                                | 2048 1939G>A | 3     |
| X59834 | X59834 | 138290 | GEN-M4  | Glutamate-ammonia ligase (glutamine synthase)                                | 2694 2585C>G | 3     |
| X59847 | X59847 | 308840 | GEN-3A5 | H.sapiens mRNA for neural cell adhesion molecule L1                          | 855 855C>T   | S     |
| X61157 | X61157 | 109635 | GEN-23  | Adrenergic receptor (Beta kinase 1-phosphorylates beta adrenergic receptor ) | 203 96A>C    | S     |
| X61157 | X61157 | 109635 | GEN-23  | Adrenergic receptor (Beta kinase 1-phosphorylates beta adrenergic receptor ) | 1372 1265A>G | H422R |
| X61157 | X61157 | 109635 | GEN-23  | Adrenergic receptor (Beta kinase 1-phosphorylates beta adrenergic receptor ) | 1501 1394G>A | R465K |

|        |        |        |         |                                                                                    |              |       |
|--------|--------|--------|---------|------------------------------------------------------------------------------------|--------------|-------|
| X61157 | X61157 | 109635 | GEN-23  | Adrenergic receptor (Beta<br>kinase 1-phosphorylates<br>beta adrenergic receptor ) | 1766 1659C>T | S     |
| X61157 | X61157 | 109635 | GEN-23  | Adrenergic receptor (Beta<br>kinase 1-phosphorylates<br>beta adrenergic receptor ) | 1823 1716T>C | S     |
| X61157 | X61157 | 109635 | GEN-23  | Adrenergic receptor (Beta<br>kinase 1-phosphorylates<br>beta adrenergic receptor ) | 2976 2869G>A | 3     |
| X63368 | X63368 | 604139 | GEN-MD  | DNAJ PROTEIN                                                                       | 2593 2568C>A | 3     |
| X63522 | X63522 | 180246 | GEN-75  | HOMOLOG HSJ1                                                                       | 1331 1152T>C | S     |
| X64878 | X64878 | 167055 | GEN-24  | MHC class I promoter<br>binding protein                                            | 4048 3681A>C | 3     |
| X65019 | X65019 | 147678 | GEN-6G  | Oxytocin receptor                                                                  | 51 44G>A     | R15H  |
| X65019 | X65019 | 147678 | GEN-6G  | INTERLEUKIN 1 BETA<br>CONVERTASE                                                   |              |       |
| X65019 | X65019 | 147678 | GEN-6G  | INTERLEUKIN 1 BETA<br>CONVERTASE                                                   | 116 109A>C   | K37Q  |
| X65019 | X65019 | 147678 | GEN-6G  | INTERLEUKIN 1 BETA<br>CONVERTASE                                                   | 261 254G>A   | G85E  |
| NTRK1  | X66397 | 191315 | GEN-3GN | PRECUSOR                                                                           | 2632 2335G>A | V779I |
| X66403 | X66403 | 100725 | GEN-5D  | H.sapiens tpr mRNA                                                                 | 2236 2225G>T | 3     |
| X66403 | X66403 | 100725 | GEN-5D  | Nicotinic, Cholinergic<br>receptor epsilon<br>polypeptide                          | 2333 2322A>G | 3     |
| X66403 | X66403 | 100725 | GEN-5D  | Nicotinic, Cholinergic<br>receptor epsilon<br>polypeptide                          | 2364 2353G>T | 3     |
| X69117 | X69117 | 109636 | GEN-5G  | Nicotinic, Cholinergic<br>receptor epsilon<br>polypeptide                          | 1182 1182T>C | S     |
| X69117 | X69117 | 109636 | GEN-5G  | BETA-ADRENERGIC<br>RECEPTOR KINASE 2                                               | 1609 1609G>A | E537K |
| X70811 | X70811 | 109691 | GEN-3KK | BETA-ADRENERGIC<br>RECEPTOR KINASE 2                                               | 315 190T>C   | W64R  |
| X71490 | X71490 | 108746 | GEN-MX  | beta-3-adrenergic receptor<br>ATPase, H+ transporting,                             | 1247 991C>A  | 3     |

|        |        |        |         |                                                                                                                        |              |       |
|--------|--------|--------|---------|------------------------------------------------------------------------------------------------------------------------|--------------|-------|
| X71490 | X71490 | 108746 | GEN-MX  | lysosomal (vacuolar proton pump) 31kD<br>ATPase, H <sup>+</sup> transporting,<br>lysosomal (vacuolar proton pump) 31kD | 1555 1299C>A | 3     |
| NOS2A  | X73029 | 163730 | GEN-3LW | H.sapiens mRNA for nitric oxide synthase                                                                               | 1380 1155C>T | S     |
| NOS2A  | X73029 | 163730 | GEN-3LW | H.sapiens mRNA for nitric oxide synthase                                                                               | 1503 1278C>T | S     |
| NOS2A  | X73029 | 163730 | GEN-3LW | H.sapiens mRNA for nitric oxide synthase                                                                               | 2048 1823C>T | S608L |
| NOS2A  | X73029 | 163730 | GEN-3LW | H.sapiens mRNA for nitric oxide synthase                                                                               | 2287 2062G>A | G688S |
| NOS2A  | X73029 | 163730 | GEN-3LW | H.sapiens mRNA for nitric oxide synthase                                                                               | 2339 2114A>G | D705G |
| NOS2A  | X73029 | 163730 | GEN-3LW | H.sapiens mRNA for nitric oxide synthase                                                                               | 2583 2358T>C | S     |
| NOS2A  | X73029 | 163730 | GEN-3LW | H.sapiens mRNA for nitric oxide synthase                                                                               | 2982 2757A>G | S     |
| NOS2A  | X73029 | 163730 | GEN-3LW | H.sapiens mRNA for nitric oxide synthase                                                                               | 3022 2797C>G | R933G |
| NOS2A  | X73029 | 163730 | GEN-3LW | H.sapiens mRNA for nitric oxide synthase                                                                               | 3051 2826C>T | S     |
| NOS2A  | X73029 | 163730 | GEN-3LW | H.sapiens mRNA for nitric oxide synthase                                                                               | 3693 3468T>C | 3     |
| NOS2A  | X73029 | 163730 | GEN-3LW | H.sapiens mRNA for nitric oxide synthase                                                                               | 3715 3490G>A | 3     |
| PREP   | X74496 | 600400 | GEN-3N8 | Prolyl Endopeptidase                                                                                                   | 390 390T>C   | S     |
| PREP   | X74496 | 600400 | GEN-3N8 | Prolyl Endopeptidase                                                                                                   | 1051 1051T>G | L351V |
| PREP   | X74496 | 600400 | GEN-3N8 | Prolyl Endopeptidase                                                                                                   | 1125 1125C>T | S     |
| PREP   | X74496 | 600400 | GEN-3N8 | Prolyl Endopeptidase                                                                                                   | 1363 1363G>A | V455M |
| X75299 | X75299 | 192321 | GEN-3NU | H.sapiens HIVR mRNA for vasoactive intestinal peptide (VIP) receptor                                                   | 1915 1904T>C | 3     |
| X75299 | X75299 | 192321 | GEN-3NU | H.sapiens HIVR mRNA for vasoactive intestinal peptide (VIP) receptor                                                   | 2475 2464T>C | 3     |

|        |        |        |         |                                                                |              |       |
|--------|--------|--------|---------|----------------------------------------------------------------|--------------|-------|
| X75958 | X75958 | 600456 | GEN-3OE | H.sapiens trkB mRNA for protein-tyrosine kinase                | 30 (-68)C>G  | 5     |
| X75958 | X75958 | 600456 | GEN-3OE | H.sapiens trkB mRNA for protein-tyrosine kinase                | 2010 1913A>G | 3     |
| X75958 | X75958 | 600456 | GEN-3OE | H.sapiens trkB mRNA for protein-tyrosine kinase                | 2101 2004C>T | 3     |
| X76228 | X76228 | 108746 | GEN-N6  | ATPase, H+ transporting, lysosomal (vacuolar proton pump) 31kD | 46 (-30)G>A  | 5     |
| X76228 | X76228 | 108746 | GEN-N6  | ATPase, H+ transporting, lysosomal (vacuolar proton pump) 31kD | 1023 948A>G  | 3     |
| X76228 | X76228 | 108746 | GEN-N6  | ATPase, H+ transporting, lysosomal (vacuolar proton pump) 31kD | 1143 1068C>T | 3     |
| LIPA   | X76488 | 278000 | GEN-3P2 | H.sapiens mRNA for lysosomal acid lipase                       | 191 46A>C    | T16P  |
| LIPA   | X76488 | 278000 | GEN-3P2 | H.sapiens mRNA for lysosomal acid lipase                       | 212 67G>A    | G23R  |
| LIPA   | X76488 | 278000 | GEN-3P2 | H.sapiens mRNA for lysosomal acid lipase                       | 967 822G>A   | M274I |
| LIPA   | X76488 | 278000 | GEN-3P2 | H.sapiens mRNA for lysosomal acid lipase                       | 1531 1386C>T | 3     |
| LIPA   | X76488 | 278000 | GEN-3P2 | H.sapiens mRNA for lysosomal acid lipase                       | 2254 2109A>T | 3     |
| LIPA   | X76488 | 278000 | GEN-3P2 | H.sapiens mRNA for lysosomal acid lipase                       | 2439 2294C>T | 3     |
| NMB    | X76534 | 162340 | GEN-3P5 | H.sapiens NMB mRNA                                             | 481 390A>G   | S     |
| NMB    | X76534 | 162340 | GEN-3P5 | H.sapiens NMB mRNA                                             | 2478 2387T>C | 3     |
| NMB    | X76534 | 162340 | GEN-3P5 | H.sapiens NMB mRNA                                             | 2655 2564A>C | 3     |
| MPV17  | X76538 | 600945 | GEN-3P6 | H.sapiens Mpv17 mRNA                                           | 575 548C>T   | 3     |
| X77130 | X77130 | 602548 | GEN-4FN | H.sapiens mRNA for ORL1 receptor                               | 528 351G>A   | S     |
| X77130 | X77130 | 602548 | GEN-4FN | H.sapiens mRNA for ORL1 receptor                               | 569 392A>G   | Y131C |
| X77130 | X77130 | 602548 | GEN-4FN | H.sapiens mRNA for ORL1 receptor                               | 687 510C>T   | S     |

|        |        |        |         |                                                            |               |      |
|--------|--------|--------|---------|------------------------------------------------------------|---------------|------|
| X77130 | X77130 | 602548 | GEN-4FN | H.sapiens mRNA for ORL1 receptor                           | 1303 1126C>G  | 3    |
| X77130 | X77130 | 602548 | GEN-4FN | H.sapiens mRNA for ORL1 receptor                           | 1816 1639G>T  | 3    |
| CLCN4  | X77197 | 302910 | GEN-3PO | H.sapiens mRNA for chloride channel                        | 212 (-172)C>T | 5    |
| X77533 | X77533 | 602730 | GEN-3Q3 | H.sapiens mRNA for activin type II receptor                | 1462 1458C>T  | S    |
| X77722 | X77722 | 602376 | GEN-29  | Interferon (alpha,beta, omega) receptor 2 (splice variant) | 253 28G>T     | V10F |
| X77722 | X77722 | 602376 | GEN-29  | Interferon (alpha,beta, omega) receptor 2 (splice variant) | 1128 903A>G   | S    |
| X77748 | X77748 | 601115 | GEN-3QD | Metabotropic glutamate receptor type 3                     | 384 126G>A    | S    |
| YWHAH  | X78138 | 113508 | GEN-3QU | H.sapiens 14-3-3 eta subtype mRNA                          | 953 753A>G    | 3    |
| YWHAH  | X78138 | 113508 | GEN-3QU | H.sapiens 14-3-3 eta subtype mRNA                          | 960 760G>A    | 3    |
| YWHAH  | X78138 | 113508 | GEN-3QU | H.sapiens 14-3-3 eta subtype mRNA                          | 1387 1187C>T  | 3    |
| X78282 | X78282 | 601292 | GEN-LVF | H.sapiens mRNA for aryl sulfotransferase (ST1A2)           | 895 895T>C    | 3    |
| X78520 | X78520 | 600580 | GEN-3RG | H.sapiens RNA for CLCN3                                    | 2804 2142T>C  | S    |
| X78520 | X78520 | 600580 | GEN-3RG | H.sapiens RNA for CLCN3                                    | 2822 2160A>G  | S    |
| X78706 | X78706 | 600184 | GEN-2A  | Carnitine Acetyltransferase                                | 1922 1922G>A  | 3    |
| X78706 | X78706 | 600184 | GEN-2A  | Carnitine Acetyltransferase                                | 2378 2378G>A  | 3    |
| X78706 | X78706 | 600184 | GEN-2A  | Carnitine Acetyltransferase                                | 2382 2382G>A  | 3    |
| X80818 | X80818 | 604100 | GEN-3VD | Metabotropic glutamate receptor type 4                     | 1625 1455T>C  | S    |
| X80818 | X80818 | 604100 | GEN-3VD | Metabotropic glutamate receptor type 4                     | 3060 2890A>G  | 3    |
| X83378 | X83378 | 602726 | GEN-NI  | Putative Chloride Channel                                  | 3181 3155T>G  | 3    |
| X83378 | X83378 | 602726 | GEN-NI  | Putative Chloride Channel                                  | 5041 5015G>A  | 3    |
| X83378 | X83378 | 602726 | GEN-NI  | Putative Chloride Channel                                  | 5366 5340G>A  | 3    |
| X83861 | X83861 | 176806 | GEN-5H  | Prostaglandin E receptor 3 (subtype EP3) (alternative      | 387 180C>G    | S    |

|        |        |        |         |                                                           |               |        |
|--------|--------|--------|---------|-----------------------------------------------------------|---------------|--------|
| X86681 | X86681 | 602110 | GEN-41E | H.sapiens mRNA for nucleolar protein, HNP36               | 1725 1340G>A  | 3      |
| X94552 | X94552 | 604101 | GEN-4FW | H.sapiens mRNA for metabotropic glutamate receptor type 7 | 2027 1789C>T  | S      |
| X94552 | X94552 | 604101 | GEN-4FW | H.sapiens mRNA for metabotropic glutamate receptor type 7 | 2434 2196C>T  | S      |
| X94552 | X94552 | 604101 | GEN-4FW | H.sapiens mRNA for metabotropic glutamate receptor type 7 | 2473 2235G>A  | S      |
| X97058 | X97058 | 602451 | GEN-4BB | P2 purinoceptor (P2Y6)                                    | 121 (-156)T>G | 5      |
| X97370 | X97370 | 601459 | GEN-4BM | H.sapiens mRNA for prepronociceptin                       | 167 144T>C    | S      |
| X97370 | X97370 | 601459 | GEN-4BM | H.sapiens mRNA for prepronociceptin                       | 637 614C>A    | 3      |
| X97370 | X97370 | 601459 | GEN-4BM | H.sapiens mRNA for prepronociceptin                       | 862 839C>G    | 3      |
| Y00052 | Y00052 | 123840 | GEN-SX  | Cyclophilin A                                             | 221 207C>G    | S      |
| Y00052 | Y00052 | 123840 | GEN-SX  | Cyclophilin A                                             | 268 254A>G    | D85G   |
| Y00052 | Y00052 | 123840 | GEN-SX  | Cyclophilin A                                             | 332 318C>T    | S      |
| Y00052 | Y00052 | 123840 | GEN-SX  | Cyclophilin A                                             | 627 613C>A    | 3      |
| CHGB   | Y00064 | 118920 | GEN-SZ  | Human mRNA for secretogranin I (chromogranin B)           | 2230 2118A>C  | 3      |
| Y00285 | Y00285 | 147280 | GEN-6I  | IGF-2 receptor                                            | 4613 4466G>A  | S1489N |
| Y00285 | Y00285 | 147280 | GEN-6I  | IGF-2 receptor                                            | 6371 6224C>T  | T2075M |
| Y00285 | Y00285 | 147280 | GEN-6I  | IGF-2 receptor                                            | 6813 6666C>T  | S      |
| Y00285 | Y00285 | 147280 | GEN-6I  | IGF-2 receptor                                            | 7150 7003G>A  | V2335M |
| Y00285 | Y00285 | 147280 | GEN-6I  | IGF-2 receptor                                            | 8685 8538C>A  | 3      |
| Y00749 | Y00749 | 131240 | GEN-P7  | Endothelin 1                                              | 846 594G>T    | K198N  |
| Y08110 | Y08110 | 602005 | GEN-1FK | H.sapiens mRNA for mosaic protein LR11                    | 3641 3561T>G  | S      |
| Y08110 | Y08110 | 602005 | GEN-1FK | H.sapiens mRNA for mosaic protein LR11                    | 3818 3738C>T  | S      |
| Y08110 | Y08110 | 602005 | GEN-1FK | H.sapiens mRNA for mosaic protein LR11                    | 5158 5078G>A  | S1693N |

|        |        |        |         |                                                     |              |        |
|--------|--------|--------|---------|-----------------------------------------------------|--------------|--------|
| Y08110 | Y08110 | 602005 | GEN-1FK | H.sapiens mRNA for mosaic protein LR11              | 6571 6491G>A | R2164K |
| Y08756 | Y08756 | 602164 | GEN-4EC | Serotonin 5-HT receptors                            | 765 747T>C   | S      |
| Y09561 | Y09561 | None   | GEN-4F4 | H.sapiens mRNA for P2X7 receptor                    | 835 809A>G   | H270R  |
| Y09561 | Y09561 | None   | GEN-4F4 | H.sapiens mRNA for P2X7 receptor                    | 946 920G>A   | R307Q  |
| Y09561 | Y09561 | None   | GEN-4F4 | H.sapiens mRNA for P2X7 receptor                    | 1068 1042G>A | A348T  |
| Y09561 | Y09561 | None   | GEN-4F4 | H.sapiens mRNA for P2X7 receptor                    | 1096 1070C>G | T357S  |
| Y09561 | Y09561 | None   | GEN-4F4 | H.sapiens mRNA for P2X7 receptor                    | 1405 1379A>G | Q460R  |
| Y09561 | Y09561 | None   | GEN-4F4 | H.sapiens mRNA for P2X7 receptor                    | 1589 1563C>G | H521Q  |
| Y09561 | Y09561 | None   | GEN-4F4 | H.sapiens mRNA for P2X7 receptor                    | 1590 1564G>A | V522I  |
| Y09561 | Y09561 | None   | GEN-4F4 | H.sapiens mRNA for P2X7 receptor                    | 1628 1602G>T | S      |
| Y09561 | Y09561 | None   | GEN-4F4 | H.sapiens mRNA for P2X7 receptor                    | 1759 1733G>A | R578Q  |
| Y09561 | Y09561 | None   | GEN-4F4 | H.sapiens mRNA for P2X7 receptor                    | 1772 1746G>A | S      |
| Y09567 | Y09567 | 602534 | GEN-1H3 | Homo sapiens mRNA for SNAP23A protein, complete CDS | 396 396G>A   | S      |
| Y09765 | Y09765 | 300093 | GEN-2C  | Gamma-aminobutyric acid (GABA) A receptor           | 358 304T>G   | S102A  |
| Y09765 | Y09765 | 300093 | GEN-2C  | Gamma-aminobutyric acid (GABA) A receptor           | 1768 1714T>C | 3      |
| Y09765 | Y09765 | 300093 | GEN-2C  | Gamma-aminobutyric acid (GABA) A receptor           | 1768 1714T>C | 3      |
| Y09765 | Y09765 | 300093 | GEN-2C  | Gamma-aminobutyric acid (GABA) A receptor           | 1976 1922C>T | 3      |
| Y09765 | Y09765 | 300093 | GEN-2C  | Gamma-aminobutyric acid (GABA) A receptor           | 1976 1922C>T | 3      |
| Y09765 | Y09765 | 300093 | GEN-2C  | Gamma-aminobutyric acid (GABA) A receptor           | 2470 2416T>C | 3      |
| Y09765 | Y09765 | 300093 | GEN-2C  | Gamma-aminobutyric acid (GABA) A receptor           | 2499 2445A>G | 3      |

|        |        |        |         |                                                           |              |       |
|--------|--------|--------|---------|-----------------------------------------------------------|--------------|-------|
| Y11044 | Y11044 | 603540 | GEN-1JS | Homo sapiens mRNA for GABA-BR1a (hGB1a) receptor          | 60 61G>T     | 3     |
| Y12226 | Y12226 | 603533 | GEN-1LV | H.sapiens mRNA for gamma-adaptin                          | 3264 3236T>C | 3     |
| Y12226 | Y12226 | 603533 | GEN-1LV | H.sapiens mRNA for gamma-adaptin                          | 3569 3541T>C | 3     |
| Y12226 | Y12226 | 603533 | GEN-1LV | H.sapiens mRNA for gamma-adaptin                          | 3683 3655A>G | 3     |
| Y15286 | Y15286 | None   | GEN-1TU | Homo sapiens mRNA for vacuolar proton-ATPase subunit M9.2 | 40 (-23)G>A  | 5     |
| Y15521 | Y15521 | None   | GEN-MEN | Homo sapiens ASMTL gene                                   | 1622 1622A>G | K541R |
| Z15108 | Z15108 | 176982 | GEN-1TE | H.sapiens mRNA for protein kinase C zeta                  | 246 240T>C   | S     |
| Z15108 | Z15108 | 176982 | GEN-1TE | H.sapiens mRNA for protein kinase C zeta                  | 1694 1688A>C | D563A |
| Z15108 | Z15108 | 176982 | GEN-1TE | H.sapiens mRNA for protein kinase C zeta                  | 2033 2027G>A | 3     |
| Z15108 | Z15108 | 176982 | GEN-1TE | H.sapiens mRNA for protein kinase C zeta                  | 2086 2080T>G | 3     |
| Z26649 | Z26649 | 600230 | GEN-2B5 | Phospholipase C beta-3                                    | 437 438C>T   | 3     |
| Z26649 | Z26649 | 600230 | GEN-2B5 | Phospholipase C beta-3                                    | 466 467G>A   | 3     |
| Z26649 | Z26649 | 600230 | GEN-2B5 | Phospholipase C beta-3                                    | 2664 2665C>T | 3     |
| Z31357 | Z31357 | 603943 | GEN-2GM | H.sapiens mRNA for cysteine dioxygenase type 1            | 388 134T>C   | I45T  |
| ECE1   | Z35307 | 600423 | GEN-2MA | Endothelin Converting Enzyme 1                            | 1141 1104C>T | S     |
| ECE1   | Z35307 | 600423 | GEN-2MA | Endothelin Converting Enzyme 1                            | 1627 1590T>C | S     |
| ECE1   | Z35307 | 600423 | GEN-2MA | Endothelin Converting Enzyme 1                            | 1696 1659G>A | S     |
| ECE1   | Z35307 | 600423 | GEN-2MA | Endothelin Converting Enzyme 1                            | 1946 1909G>A | V637M |
| ECE1   | Z35307 | 600423 | GEN-2MA | Endothelin Converting Enzyme 1                            | 2433 2396G>A | 3     |



|        |        |        |         |                                                                        |              |       |
|--------|--------|--------|---------|------------------------------------------------------------------------|--------------|-------|
| PDE4C  | Z46632 | 600128 | GEN-2X2 | H.sapiens HSPDE4C1 gene for 3,5-cyclic AMP phosphodiesterase           | 280 169C>T   | R57C  |
| PDE4C  | Z46632 | 600128 | GEN-2X2 | H.sapiens HSPDE4C1 gene for 3,5-cyclic AMP phosphodiesterase           | 1142 1031G>A | R344Q |
| Z69028 | Z69028 | 601644 | GEN-3J4 | H.sapiens mRNA for beta 2 isoform of 61 kDa regulatory subunit of PP2A | 1681 1612A>T | 3     |
| PAM    | M37721 | 170270 | GEN-2OK | Human peptidylglycine alpha-amidating monooxygenase mRNA, complete cds | 3183 2995T>A | 3     |
| PAM    | M37721 | 170270 | GEN-2OK | Human peptidylglycine alpha-amidating monooxygenase mRNA, complete cds | 3530 3342A>G | 3     |
| PACE   | X17094 | 136950 | GEN-1ZV | Human fur mRNA for furin                                               | 399 183C>T   | S     |
| PACE   | X17094 | 136950 | GEN-1ZV | Human fur mRNA for furin                                               | 1692 1476C>T | S     |
| PACE   | X17094 | 136950 | GEN-1ZV | Human fur mRNA for furin                                               | 2067 1851C>G | S     |
| PACE   | X17094 | 136950 | GEN-1ZV | Human fur mRNA for furin                                               | 2725 2509T>C | 3     |
| PACE   | X17094 | 136950 | GEN-1ZV | Human fur mRNA for furin                                               | 2855 2639C>A | 3     |
| PACE   | X17094 | 136950 | GEN-1ZV | Human fur mRNA for furin                                               | 2988 2772G>A | 3     |
| PACE   | X17094 | 136950 | GEN-1ZV | Human fur mRNA for furin                                               | 3234 3018C>T | 3     |
| PACE   | X17094 | 136950 | GEN-1ZV | Human fur mRNA for furin                                               | 3625 3409A>G | 3     |
| PACE   | X17094 | 136950 | GEN-1ZV | Human fur mRNA for furin                                               | 3883 3667C>T | 3     |
| PACE   | X17094 | 136950 | GEN-1ZV | Human fur mRNA for furin                                               | 4053 3837A>G | 3     |

Table 14.  
Identified  
Variances

SD-144146.1

In Genes  
and  
Related  
Pathways  
Identified  
in  
Pharmacokinetic  
and  
Pharmacodynamic  
Parameters of  
Candidate  
Therapeutic  
Interventions

|         |         |        |         |                                                                                      |      |         |       |
|---------|---------|--------|---------|--------------------------------------------------------------------------------------|------|---------|-------|
| AAC2    | D90040  | 243400 | GEN-465 | Human mRNA for<br>arylamine N-<br>acetyltransferase (EC<br>2.3.1.5)                  | 232  | 191G>A  | R64Q  |
| AAC2    | D90040  | 243400 | GEN-465 | Human mRNA for<br>arylamine N-<br>acetyltransferase (EC<br>2.3.1.5)                  | 323  | 282C>T  | S     |
| AAC2    | D90040  | 243400 | GEN-465 | Human mRNA for<br>arylamine N-<br>acetyltransferase (EC<br>2.3.1.5)                  | 844  | 803A>G  | K268R |
| AB00081 | AB00081 | 602550 | GEN-14E | Human mRNA for<br>BMAL1b, complete cds                                               | 1084 | 1044C>A | S     |
| AB00379 | AB00379 | 603797 | GEN-1F9 | Homo sapiens mRNA for<br>keratan sulfate Gal-6-<br>sulfotransferase, complete<br>cds | 1617 | 1251G>A | 3     |
| AB00379 | AB00379 | 603797 | GEN-1F9 | Homo sapiens mRNA for<br>keratan sulfate Gal-6-<br>sulfotransferase, complete<br>cds | 1643 | 1277G>A | 3     |

|         |         |        |             |                                                                                                                 |      |         |        |
|---------|---------|--------|-------------|-----------------------------------------------------------------------------------------------------------------|------|---------|--------|
| AB00485 | AB00485 | 603608 | GEN-<br>KV6 | Homo sapiens mRNA for<br>carbonyl reductase 3,<br>complete cds                                                  | 730  | 730G>A  | V244M  |
| AB00528 | AB00528 | 300135 | GEN-<br>KVU | Homo sapiens mRNA for<br>ABC transporter 7 protein,<br>complete cds                                             | 2137 | 2069A>T | H690L  |
| AB01467 | AB01467 | None   | GEN-L22     | Homo sapiens GN6ST<br>mRNA for N-<br>acetylglucosamine-6-O-<br>sulfotransferase<br>(GlcNAc6ST), complete<br>cds | 1578 | 1189G>T | V397L  |
| AB01467 | AB01467 | None   | GEN-L22     | Homo sapiens GN6ST<br>mRNA for N-<br>acetylglucosamine-6-O-<br>sulfotransferase<br>(GlcNAc6ST), complete<br>cds | 2335 | 1946T>C | 3      |
| AB01505 | AB01505 | 603377 | GEN-<br>L2D | Homo sapiens mRNA for<br>OCTN2, complete cds                                                                    | 1101 | 978G>A  | S      |
| ABC3    | X97187  | 601615 | GEN-4BI     | H.sapiens mRNA for ABC-<br>C transporter                                                                        | 4671 | 4324G>T | V1442F |
| ABC3    | X97187  | 601615 | GEN-4BI     | H.sapiens mRNA for ABC-<br>C transporter                                                                        | 5075 | 4728G>A | S      |
| ADH2    | M24317  | 103720 | GEN-<br>28A | Human class I alcohol<br>dehydrogenase (ADH2)<br>beta-1 subunit mRNA,<br>complete cds                           | 817  | 787G>A  | V263M  |
| ADH3    | M12272  | 103730 | GEN-<br>1LU | Homo sapiens alcohol<br>dehydrogenase class I<br>gamma subunit (ADH3)<br>mRNA, complete cds                     | 1128 | 1048A>G | I350V  |
| ADH4    | M15943  | 103740 | GEN-<br>1UM | Human class II alcohol<br>dehydrogenase (ADH4) pi<br>subunit mRNA, complete<br>cds                              | 826  | 765G>T  | S      |
| ADH4    | M15943  | 103740 | GEN-<br>1UM | Human class II alcohol<br>dehydrogenase (ADH4) pi<br>subunit mRNA, complete<br>cds                              | 1389 | 1328T>C | 3      |
| ADH5    | M29872  | 103710 | GEN-        | Human alcohol                                                                                                   | 1029 | 1025G>A | S342N  |

|          |          |        |         |         |                                                                                       |      |         |       |
|----------|----------|--------|---------|---------|---------------------------------------------------------------------------------------|------|---------|-------|
| ADH5     | M29872   | 103710 | GEN-2EU | 2EU     | dehydrogenase class III (ADH5) mRNA, complete cds                                     | 1375 | 1371T>C | 3     |
| AF001437 | AF001437 | 245349 | GEN-9T  | GEN-9T  | Human alcohol dehydrogenase class III (ADH5) mRNA, complete cds                       | 75   | 67T>C   | C23R  |
| AF001437 | AF001437 | 245349 | GEN-9T  | GEN-9T  | Dihydrolipoamide S-acetyltransferase (E2 component of pyruvate dehydrogenase complex) | 116  | 108C>T  | S     |
| AF001437 | AF001437 | 245349 | GEN-9T  | GEN-9T  | Dihydrolipoamide S-acetyltransferase (E2 component of pyruvate dehydrogenase complex) | 759  | 751T>G  | S251A |
| AF001437 | AF001437 | 245349 | GEN-9T  | GEN-9T  | Dihydrolipoamide S-acetyltransferase (E2 component of pyruvate dehydrogenase complex) | 806  | 798C>T  | S     |
| AF001437 | AF001437 | 245349 | GEN-9T  | GEN-9T  | Dihydrolipoamide S-acetyltransferase (E2 component of pyruvate dehydrogenase complex) | 866  | 858T>C  | S     |
| AF001437 | AF001437 | 245349 | GEN-9T  | GEN-9T  | Dihydrolipoamide S-acetyltransferase (E2 component of pyruvate dehydrogenase complex) | 2000 | 1992G>T | 3     |
| AF001437 | AF001437 | 245349 | GEN-9T  | GEN-9T  | Dihydrolipoamide S-acetyltransferase (E2 component of pyruvate dehydrogenase complex) | 2158 | 2150C>A | 3     |
| AF001945 | AF001945 | 601691 | GEN-17Z | GEN-17Z | Homo sapiens rim ABC transporter (ABCR) mRNA, complete cds                            | 2725 | 2644G>A | G882S |
| AF001945 | AF001945 | 601691 | GEN-17Z | GEN-17Z | Homo sapiens rim ABC transporter (ABCR) mRNA, complete cds                            | 5136 | 5055C>T | S     |

|          |          |        |         |                                                                                                                    |      |           |       |
|----------|----------|--------|---------|--------------------------------------------------------------------------------------------------------------------|------|-----------|-------|
| AF009746 | AF009746 | 603214 | GEN-1HZ | Homo sapiens peroxisomal membrane protein 69 (PMP69) mRNA, complete cds                                            | 961  | 910G>A    | A304T |
| AF009746 | AF009746 | 603214 | GEN-1HZ | Homo sapiens peroxisomal membrane protein 69 (PMP69) mRNA, complete cds                                            | 1895 | 1844A>G   | 3     |
| AF009746 | AF009746 | 603214 | GEN-1HZ | Homo sapiens peroxisomal membrane protein 69 (PMP69) mRNA, complete cds                                            | 2134 | 2083T>G   | 3     |
| AF019386 | AF019386 | None   | GEN-231 | Homo sapiens heparan sulfate 3-O-sulfotransferase-1 precursor (3OST1) mRNA, complete cds                           | 79   | (-40)C>G  | 5     |
| AF026947 | AF026947 | 603418 | GEN-261 | Homo sapiens aflatoxin aldehyde reductase AFAR mRNA, complete cds                                                  | 1013 | 936T>C    | S     |
| AF026947 | AF026947 | 603418 | GEN-261 | Homo sapiens aflatoxin aldehyde reductase AFAR mRNA, complete cds                                                  | 1078 | 1001A>G   | 3     |
| AF027302 | AF027302 | 603429 | GEN-27T | Homo sapiens TNF-alpha stimulated ABC protein (ABC50) mRNA, complete cds                                           | 3075 | 2981T>C   | 3     |
| AF028738 | AF028738 | 602631 | GEN-2F6 | Homo sapiens imprinted multi-membrane spanning polyspecific transporter-related protein (IMPT1) mRNA, complete cds | 34   | (-209)A>C | 5     |
| AF028738 | AF028738 | 602631 | GEN-2F6 | Homo sapiens imprinted multi-membrane spanning polyspecific transporter-related protein (IMPT1) mRNA, complete cds | 210  | (-33)G>A  | 5     |
| AF028738 | AF028738 | 602631 | GEN-2F6 | Homo sapiens imprinted multi-membrane spanning polyspecific transporter-related protein (IMPT1) mRNA, complete cds | 229  | (-14)A>G  | 5     |

|          |          |        |             |                                                                                                                                 |      |        |       |
|----------|----------|--------|-------------|---------------------------------------------------------------------------------------------------------------------------------|------|--------|-------|
| AF028738 | AF028738 | 602631 | GEN-<br>2F6 | mRNA, complete cds<br>Homo sapiens imprinted<br>multi-membrane spanning<br>polyspecific transporter-<br>related protein (IMPT1) | 375  | 133T>G | F45V  |
| AF028738 | AF028738 | 602631 | GEN-<br>2F6 | mRNA, complete cds<br>Homo sapiens imprinted<br>multi-membrane spanning<br>polyspecific transporter-<br>related protein (IMPT1) | 875  | 633A>C | E211D |
| AF028738 | AF028738 | 602631 | GEN-<br>2F6 | mRNA, complete cds<br>Homo sapiens imprinted<br>multi-membrane spanning<br>polyspecific transporter-<br>related protein (IMPT1) | 881  | 639A>G | S     |
| AF028738 | AF028738 | 602631 | GEN-<br>2F6 | mRNA, complete cds<br>Homo sapiens imprinted<br>multi-membrane spanning<br>polyspecific transporter-<br>related protein (IMPT1) | 883  | 641G>C | G214A |
| AF028738 | AF028738 | 602631 | GEN-<br>2F6 | mRNA, complete cds<br>Homo sapiens imprinted<br>multi-membrane spanning<br>polyspecific transporter-<br>related protein (IMPT1) | 919  | 677A>G | K226R |
| AF028738 | AF028738 | 602631 | GEN-<br>2F6 | mRNA, complete cds<br>Homo sapiens imprinted<br>multi-membrane spanning<br>polyspecific transporter-<br>related protein (IMPT1) | 927  | 685T>C | S     |
| AF028738 | AF028738 | 602631 | GEN-<br>2F6 | mRNA, complete cds<br>Homo sapiens imprinted<br>multi-membrane spanning<br>polyspecific transporter-<br>related protein (IMPT1) | 935  | 693A>G | S     |
| AF028738 | AF028738 | 602631 | GEN-<br>2F6 | mRNA, complete cds<br>Homo sapiens imprinted<br>multi-membrane spanning<br>polyspecific transporter-<br>related protein (IMPT1) | 1004 | 762A>G | S     |

|          |          |        |             |                                                                                                                    |      |         |       |
|----------|----------|--------|-------------|--------------------------------------------------------------------------------------------------------------------|------|---------|-------|
| AF028738 | AF028738 | 602631 | GEN-<br>2F6 | Homo sapiens imprinted multi-membrane spanning polyspecific transporter-related protein (IMPT1) mRNA, complete cds | 1017 | 775A>C  | K259Q |
| AF028738 | AF028738 | 602631 | GEN-<br>2F6 | Homo sapiens imprinted multi-membrane spanning polyspecific transporter-related protein (IMPT1) mRNA, complete cds | 1106 | 864A>G  | S     |
| AF028738 | AF028738 | 602631 | GEN-<br>2F6 | Homo sapiens imprinted multi-membrane spanning polyspecific transporter-related protein (IMPT1) mRNA, complete cds | 1119 | 877G>C  | G293R |
| AF028738 | AF028738 | 602631 | GEN-<br>2F6 | Homo sapiens imprinted multi-membrane spanning polyspecific transporter-related protein (IMPT1) mRNA, complete cds | 1124 | 882A>C  | S     |
| AF028738 | AF028738 | 602631 | GEN-<br>2F6 | Homo sapiens imprinted multi-membrane spanning polyspecific transporter-related protein (IMPT1) mRNA, complete cds | 1166 | 924G>C  | W308C |
| AF038175 | AF038175 | None   | GEN-<br>2QM | Homo sapiens clone 23819 white protein homolog mRNA, partial cds                                                   | 1100 | 1100G>A | 3     |
| AF055025 | AF055025 | 300095 | GEN-<br>32U | Homo sapiens clone 24776 mRNA sequence                                                                             | 784  | 785A>G  | 3     |
| AF055025 | AF055025 | 300095 | GEN-<br>32U | Homo sapiens clone 24776 mRNA sequence                                                                             | 2021 | 2022A>T | 3     |
| AF058056 | AF058056 | None   | GEN-<br>MNJ | Homo sapiens monocarboxylate transporter 2 (hMCT2) mRNA, complete cds                                              | 200  | 73G>A   | A25T  |
| AF058056 | AF058056 | None   | GEN-<br>MNJ | Homo sapiens monocarboxylate transporter 2 (hMCT2) mRNA, complete cds                                              | 203  | 76G>A   | A26T  |
| AF058056 | AF058056 | None   | GEN-        | Homo sapiens mRNA, complete cds                                                                                    | 588  | 461G>A  | S154N |

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|          |          |        |             |                                                                                           |      |          |       |
|----------|----------|--------|-------------|-------------------------------------------------------------------------------------------|------|----------|-------|
| AJ130718 | AJ130718 | None   | GEN-<br>LDO | Homo sapiens mRNA for glycoprotein-associated amino acid transporter y <sup>+</sup> -LAT1 | 1820 | 1527G>A  | S     |
| ALDH10   | L47162   | 270200 | GEN-2XI     | Human fatty aldehyde dehydrogenase (FALDH) mRNA, complete cds                             | 1609 | 1446A>T  | S     |
| ALDH3    | M74542   | 100660 | GEN-3N9     | Human aldehyde dehydrogenase type III (ALDHIII) mRNA, complete cds                        | 1616 | 1574A>G  | 3     |
| ALDH6    | U07919   | 600463 | GEN-1F5     | Human aldehyde dehydrogenase 6 mRNA, complete cds                                         | 2453 | 2401A>G  | 3     |
| ALDH6    | U07919   | 600463 | GEN-1F5     | Human aldehyde dehydrogenase 6 mRNA, complete cds                                         | 3396 | 3344C>T  | 3     |
| ALDH6    | U07919   | 600463 | GEN-1F5     | Human aldehyde dehydrogenase 6 mRNA, complete cds                                         | 3397 | 3345G>A  | 3     |
| ARNT     | M69238   | 126110 | GEN-3JH     | Human aryl hydrocarbon receptor nuclear translocator (ARNT) mRNA, complete cds            | 623  | 567G>C   | S     |
| ARSB     | M32373   | 253200 | GEN-2J0     | Human arylsulfatase B (ASB) mRNA, complete cds                                            | 1631 | 1072G>A  | V358M |
| ARSE     | X83573   | 300180 | GEN-3Y8     | Homo sapiens ARSE gene, complete CDS                                                      | 1759 | 1692C>T  | S     |
| ARSE     | X83573   | 300180 | GEN-3Y8     | Homo sapiens ARSE gene, complete CDS                                                      | 1795 | 1728G>A  | S     |
| CAT      | X04076   | 115500 | GEN-13P     | Human kidney mRNA for catalase                                                            | 51   | (-20)T>C | 5     |
| CAT      | X04076   | 115500 | GEN-13P     | Human kidney mRNA for catalase                                                            | 218  | 148C>T   | L50F  |
| CAT      | X04076   | 115500 | GEN-13P     | Human kidney mRNA for catalase                                                            | 1237 | 1167T>C  | S     |
| CAT      | X04076   | 115500 | GEN-13P     | Human kidney mRNA for catalase                                                            | 1325 | 1255C>T  | S     |
| CAT      | X04076   | 115500 | GEN-13P     | Human kidney mRNA for catalase                                                            | 2131 | 2061A>C  | 3     |

|      |        |        |         |                                                                                            |      |         |       |
|------|--------|--------|---------|--------------------------------------------------------------------------------------------|------|---------|-------|
| CBG  | J02943 | 122500 | GEN-Y2  | Human corticosteroid binding globulin mRNA, complete cds                                   | 106  | 71A>T   | D24V  |
| CBG  | J02943 | 122500 | GEN-Y2  | Human corticosteroid binding globulin mRNA, complete cds                                   | 971  | 936T>C  | S     |
| CBG  | J02943 | 122500 | GEN-Y2  | Human corticosteroid binding globulin mRNA, complete cds                                   | 1229 | 1194G>A | S     |
| CBR  | J04056 | 114830 | GEN-130 | Human carbonyl reductase mRNA, complete cds                                                | 1060 | 967G>A  | 3     |
| CBS  | L00972 | 236200 | GEN-UV  | Human cystathionine-beta-synthase (CBS) mRNA                                               | 1022 | 1023T>C | 3     |
| CBS  | L00972 | 236200 | GEN-UV  | Human cystathionine-beta-synthase (CBS) mRNA                                               | 2001 | 2002C>T | 3     |
| CBS  | L00972 | 236200 | GEN-UV  | Human cystathionine-beta-synthase (CBS) mRNA                                               | 2278 | 2279G>A | 3     |
| CBS  | L00972 | 236200 | GEN-UV  | Human cystathionine-beta-synthase (CBS) mRNA                                               | 2358 | 2359G>C | 3     |
| CBS  | L00972 | 236200 | GEN-UV  | Human cystathionine-beta-synthase (CBS) mRNA                                               | 2524 | 2525T>C | 3     |
| CBS  | L00972 | 236200 | GEN-UV  | Human cystathionine-beta-synthase (CBS) mRNA                                               | 2545 | 2546C>T | 3     |
| CEL  | M85201 | 114841 | GEN-404 | Human cholesterol esterase mRNA, complete cds                                              | 566  | 558T>C  | S     |
| CEL  | M85201 | 114841 | GEN-404 | Human cholesterol esterase mRNA, complete cds                                              | 1306 | 1298G>A | S433N |
| CEL  | M85201 | 114841 | GEN-404 | Human cholesterol esterase mRNA, complete cds                                              | 1826 | 1818C>T | S     |
| CFTR | M28668 | 602421 | GEN-2DF | Human cystic fibrosis mRNA, encoding a presumed transmembrane conductance regulator (CFTR) | 2729 | 2597G>A | C866Y |
| CFTR | M28668 | 602421 | GEN-2DF | Human cystic fibrosis mRNA, encoding a presumed transmembrane conductance regulator        | 5826 | 5694T>C | 3     |

|         |        |        |         |                                                                             |      |         |       |
|---------|--------|--------|---------|-----------------------------------------------------------------------------|------|---------|-------|
| CPA1    | X67318 | 114850 | GEN-3HJ | (CFTR)<br>H.sapiens mRNA for<br>procarboxypeptidase A1                      | 172  | 165G>C  | S     |
| CPA1    | X67318 | 114850 | GEN-3HJ | H.sapiens mRNA for<br>procarboxypeptidase A1                                | 498  | 491C>G  | T164R |
| CPA1    | X67318 | 114850 | GEN-3HJ | H.sapiens mRNA for<br>procarboxypeptidase A1                                | 629  | 622G>A  | A208T |
| CRYZ    | L13278 | 123691 | GEN-1NZ | Homo sapiens zeta-<br>crystallin/quinone<br>reductase mRNA,<br>complete cds | 64   | 54G>A   | S     |
| CRYZ    | L13278 | 123691 | GEN-1NZ | Homo sapiens zeta-<br>crystallin/quinone<br>reductase mRNA,<br>complete cds | 902  | 892G>A  | V298M |
| CRYZ    | L13278 | 123691 | GEN-1NZ | Homo sapiens zeta-<br>crystallin/quinone<br>reductase mRNA,<br>complete cds | 1229 | 1219A>G | 3     |
| CTH     | S52028 | 219500 | GEN-33F | cystathionine gamma-lyase<br>{clone HCL-1} (human,<br>liver, mRNA, 1194 nt) | 1109 | 1076T>G | I359S |
| CYP11B2 | D13752 | 124080 | GEN-CCD | Human CYP11B2 gene for<br>steroid 18-hydroxylase,<br>complete cds           | 1600 | 1593G>A | 3     |
| CYP1B1  | U03688 | 601771 | GEN-11Y | Human dioxin-inducible<br>cytochrome P450<br>(CYP1B1) mRNA,<br>complete cds | 488  | 142C>G  | R48G  |
| CYP1B1  | U03688 | 601771 | GEN-11Y | Human dioxin-inducible<br>cytochrome P450<br>(CYP1B1) mRNA,<br>complete cds | 701  | 355G>T  | A119S |
| CYP1B1  | U03688 | 601771 | GEN-11Y | Human dioxin-inducible<br>cytochrome P450<br>(CYP1B1) mRNA,<br>complete cds | 2673 | 2327G>T | 3     |
| CYP21   | M17252 | 201910 | GEN-201 | Human cytochrome<br>P450c21 mRNA, 3 end                                     | 224  | 224G>A  | R75H  |
| CYP21   | M17252 | 201910 | GEN-201 | Human cytochrome<br>P450c21 mRNA, 3 end                                     | 330  | 330C>T  | S     |

|       |        |        |         |                                                                            |      |         |       |
|-------|--------|--------|---------|----------------------------------------------------------------------------|------|---------|-------|
| CYP21 | M17252 | 201910 | GEN-201 | Human cytochrome P450c21 mRNA, 3 end                                       | 745  | 745T>C  | 3     |
| CYP51 | U23942 | 601637 | GEN-27K | Human lanosterol 14-demethylase cytochrome P450 (CYP51) mRNA, complete cds | 766  | 644G>A  | C215Y |
| CYP51 | U23942 | 601637 | GEN-27K | Human lanosterol 14-demethylase cytochrome P450 (CYP51) mRNA, complete cds | 894  | 772C>T  | R258C |
| CYP51 | U23942 | 601637 | GEN-27K | Human lanosterol 14-demethylase cytochrome P450 (CYP51) mRNA, complete cds | 912  | 790C>T  | R264W |
| CYP51 | U23942 | 601637 | GEN-27K | Human lanosterol 14-demethylase cytochrome P450 (CYP51) mRNA, complete cds | 1476 | 1354C>T | R452C |
| CYP51 | U23942 | 601637 | GEN-27K | Human lanosterol 14-demethylase cytochrome P450 (CYP51) mRNA, complete cds | 1616 | 1494G>A | S     |
| CYP51 | U23942 | 601637 | GEN-27K | Human lanosterol 14-demethylase cytochrome P450 (CYP51) mRNA, complete cds | 1836 | 1714C>A | 3     |
| CYP51 | U23942 | 601637 | GEN-27K | Human lanosterol 14-demethylase cytochrome P450 (CYP51) mRNA, complete cds | 2283 | 2161G>T | 3     |
| CYP51 | U23942 | 601637 | GEN-27K | Human lanosterol 14-demethylase cytochrome P450 (CYP51) mRNA, complete cds | 2445 | 2323T>C | 3     |
| CYP51 | U23942 | 601637 | GEN-27K | Human lanosterol 14-demethylase cytochrome P450 (CYP51) mRNA, complete cds | 2507 | 2385G>A | 3     |
| CYP51 | U23942 | 601637 | GEN-27K | Human lanosterol 14-demethylase cytochrome P450 (CYP51) mRNA, complete cds | 2556 | 2434T>A | 3     |

|        |        |        |         |                                                                               |      |            |       |
|--------|--------|--------|---------|-------------------------------------------------------------------------------|------|------------|-------|
| CYP51  | U23942 | 601637 | GEN-27K | complete cds<br>Human lanosterol 14-demethylase cytochrome P450 (CYP51) mRNA, | 2665 | 2543G>A    | 3     |
| D13138 | D13138 | 179780 | GEN-1NW | complete cds<br>Human mRNA for dipeptidase                                    | 566  | 523T>G     | S175A |
| D17793 | D17793 | None   | GEN-20Q | Human mRNA for KIAA0119 gene, complete cds                                    | 66   | 15G>C      | Q5H   |
| D17793 | D17793 | None   | GEN-20Q | Human mRNA for KIAA0119 gene, complete cds                                    | 141  | 90G>A      | S     |
| D17793 | D17793 | None   | GEN-20Q | Human mRNA for KIAA0119 gene, complete cds                                    | 363  | 312A>G     | S     |
| D17793 | D17793 | None   | GEN-20Q | Human mRNA for KIAA0119 gene, complete cds                                    | 980  | 929G>C     | S310T |
| D87292 | D87292 | 180370 | GEN-42Y | Human mRNA for rhodanese, complete cds                                        | 816  | 768C>T     | S     |
| D87292 | D87292 | 180370 | GEN-42Y | Human mRNA for rhodanese, complete cds                                        | 946  | 898G>A     | 3     |
| D87845 | D87845 | 602344 | GEN-44C | Human mRNA for platelet-activating factor acetylhydrolase 2, complete cds     | 2299 | 2096G>A    | 3     |
| D87845 | D87845 | 602344 | GEN-44C | Human mRNA for platelet-activating factor acetylhydrolase 2, complete cds     | 2332 | 2129A>G    | 3     |
| D89078 | D89078 | 601531 | GEN-7   | complete cds<br>P2Y7 purinoceptor                                             | 434  | (-1284)A>T | 5     |
| D89078 | D89078 | 601531 | GEN-7   | P2Y7 purinoceptor                                                             | 889  | (-829)G>C  | 5     |
| D89078 | D89078 | 601531 | GEN-7   | P2Y7 purinoceptor                                                             | 1156 | (-562)G>C  | 5     |
| D89078 | D89078 | 601531 | GEN-7   | P2Y7 purinoceptor                                                             | 2644 | 927T>C     | S     |
| D89078 | D89078 | 601531 | GEN-7   | P2Y7 purinoceptor                                                             | 2920 | 1203A>G    | 3     |
| D90041 | D90041 | 108345 | GEN-464 | Human liver arylamine N-acetyltransferase (EC 2.3.1.5) gene                   | 591  | 445G>A     | V149I |
| D90041 | D90041 | 108345 | GEN-464 | Human liver arylamine N-                                                      | 1240 | 1094C>A    | 3     |

|      |        |        |         |                                                                                                 |      |        |       |
|------|--------|--------|---------|-------------------------------------------------------------------------------------------------|------|--------|-------|
| DDH1 | U05598 | 600450 | GEN-184 | acetyltransferase (EC 2.3.1.5) gene<br>Human dihydrodiol<br>dehydrogenase mRNA,<br>complete cds | 38   | 15C>T  | S     |
| DDH1 | U05598 | 600450 | GEN-184 | Human dihydrodiol<br>dehydrogenase mRNA,<br>complete cds                                        | 282  | 259A>T | S87C  |
| DDH1 | U05598 | 600450 | GEN-184 | Human dihydrodiol<br>dehydrogenase mRNA,<br>complete cds                                        | 350  | 327C>T | S     |
| DDH1 | U05598 | 600450 | GEN-184 | Human dihydrodiol<br>dehydrogenase mRNA,<br>complete cds                                        | 365  | 342T>C | S     |
| DDH1 | U05598 | 600450 | GEN-184 | Human dihydrodiol<br>dehydrogenase mRNA,<br>complete cds                                        | 464  | 441G>A | S     |
| DDH1 | U05598 | 600450 | GEN-184 | Human dihydrodiol<br>dehydrogenase mRNA,<br>complete cds                                        | 474  | 451A>G | M151V |
| DDH1 | U05598 | 600450 | GEN-184 | Human dihydrodiol<br>dehydrogenase mRNA,<br>complete cds                                        | 532  | 509A>G | H170R |
| DDH1 | U05598 | 600450 | GEN-184 | Human dihydrodiol<br>dehydrogenase mRNA,<br>complete cds                                        | 538  | 515T>A | L172Q |
| DDH1 | U05598 | 600450 | GEN-184 | Human dihydrodiol<br>dehydrogenase mRNA,<br>complete cds                                        | 689  | 666T>C | S     |
| DDH1 | U05598 | 600450 | GEN-184 | Human dihydrodiol<br>dehydrogenase mRNA,<br>complete cds                                        | 806  | 783G>A | S     |
| DDH1 | U05598 | 600450 | GEN-184 | Human dihydrodiol<br>dehydrogenase mRNA,<br>complete cds                                        | 872  | 849G>T | S     |
| DDH1 | U05598 | 600450 | GEN-184 | Human dihydrodiol<br>dehydrogenase mRNA,<br>complete cds                                        | 952  | 929T>G | I310S |
| DDH1 | U05598 | 600450 | GEN-184 | Human dihydrodiol<br>dehydrogenase mRNA,<br>complete cds                                        | 1020 | 997G>A | 3     |

|        |        |        |         |                                                                                                     |      |         |       |
|--------|--------|--------|---------|-----------------------------------------------------------------------------------------------------|------|---------|-------|
| DDH1   | U05598 | 600450 | GEN-184 | Human dihydrodiol dehydrogenase mRNA, complete cds                                                  | 1035 | 1012G>A | 3     |
| DDH1   | U05598 | 600450 | GEN-184 | Human dihydrodiol dehydrogenase mRNA, complete cds                                                  | 1112 | 1089C>T | 3     |
| DHFR   | J00140 | 126060 | GEN-4E9 | Human dihydrofolate reductase gene                                                                  | 721  | 679T>A  | 3     |
| DHFR   | J00140 | 126060 | GEN-4E9 | Human dihydrofolate reductase gene                                                                  | 721  | 679T>A  | 3     |
| DHFR   | J00140 | 126060 | GEN-4E9 | Human dihydrofolate reductase gene                                                                  | 829  | 787C>T  | 3     |
| EHHADH | L07077 | 261515 | GEN-1DF | Human enoyl-CoA: hydratase 3-hydroxyacyl-CoA dehydrogenase (EHHADH) mRNA, complete cds with repeats | 1225 | 1218G>A | S     |
| EHHADH | L07077 | 261515 | GEN-1DF | Human enoyl-CoA: hydratase 3-hydroxyacyl-CoA dehydrogenase (EHHADH) mRNA, complete cds with repeats | 1823 | 1816C>A | P606T |
| ELA1   | M16631 | 130120 | GEN-1YI | Human elastase 2 mRNA, complete cds                                                                 | 510  | 489G>A  | S     |
| ELA1   | M16631 | 130120 | GEN-1YI | Human elastase 2 mRNA, complete cds                                                                 | 693  | 672G>A  | S     |
| EPHX1  | L25878 | 132810 | GEN-29Z | Homo sapiens p33/HEH epoxide hydrolase (EPHX) mRNA, complete cds                                    | 460  | 337T>C  | Y113H |
| EPHX1  | L25878 | 132810 | GEN-29Z | Homo sapiens p33/HEH epoxide hydrolase (EPHX) mRNA, complete cds                                    | 480  | 357A>G  | S     |
| EPHX1  | L25878 | 132810 | GEN-29Z | Homo sapiens p33/HEH epoxide hydrolase (EPHX) mRNA, complete cds                                    | 539  | 416A>G  | H139R |
| EPHX1  | L25878 | 132810 | GEN-29Z | Homo sapiens p33/HEH epoxide hydrolase (EPHX) mRNA, complete cds                                    | 1194 | 1071C>T | S     |
| EPHX2  | L05779 | 132811 | GEN-18A | Human cytosolic epoxide hydrolase mRNA, complete cds                                                | 1631 | 1590A>C | S     |

|       |        |        |         |                                                                        |      |         |       |
|-------|--------|--------|---------|------------------------------------------------------------------------|------|---------|-------|
| EPHX2 | L05779 | 132811 | GEN-18A | Human cytosolic epoxide hydrolase mRNA, complete cds                   | 1742 | 1701A>G | 3     |
| EPHX2 | L05779 | 132811 | GEN-18A | Human cytosolic epoxide hydrolase mRNA, complete cds                   | 1800 | 1759T>C | 3     |
| FABP2 | M10050 | 134640 | GEN-1IE | Human liver fatty acid binding protein (FABP) mRNA, complete cds       | 322  | 280G>A  | A94T  |
| FACL1 | L09229 | 152425 | GEN-1GI | Human long-chain acyl-coenzyme A synthetase (FACL1) mRNA, complete cds | 3026 | 2953G>A | 3     |
| FACL1 | L09229 | 152425 | GEN-1GI | Human long-chain acyl-coenzyme A synthetase (FACL1) mRNA, complete cds | 3083 | 3010G>A | 3     |
| GC    | M12654 | 139200 | GEN-1MN | Human serum vitamin D-binding protein (hDBP) mRNA, complete cds        | 925  | 897T>C  | S     |
| GC    | M12654 | 139200 | GEN-1MN | Human serum vitamin D-binding protein (hDBP) mRNA, complete cds        | 1324 | 1296G>T | E432D |
| GC    | M12654 | 139200 | GEN-1MN | Human serum vitamin D-binding protein (hDBP) mRNA, complete cds        | 1335 | 1307C>A | T436K |
| GC    | M12654 | 139200 | GEN-1MN | Human serum vitamin D-binding protein (hDBP) mRNA, complete cds        | 1362 | 1334G>A | R445H |
| GPX1  | Y00433 | 138320 | GEN-TJ  | Human mRNA for glutathione peroxidase (EC 1.11.1.9.)                   | 504  | 186G>A  | S     |
| GPX1  | Y00433 | 138320 | GEN-TJ  | Human mRNA for glutathione peroxidase (EC 1.11.1.9.)                   | 610  | 292C>G  | R98G  |
| GPX1  | Y00433 | 138320 | GEN-TJ  | Human mRNA for glutathione peroxidase (EC 1.11.1.9.)                   | 911  | 593C>T  | P198L |
| GPX1  | Y00433 | 138320 | GEN-TJ  | Human mRNA for glutathione peroxidase (EC 1.11.1.9.)                   | 1048 | 730A>C  | 3     |



|       |        |        |         |                                                                            |      |         |       |
|-------|--------|--------|---------|----------------------------------------------------------------------------|------|---------|-------|
| GPX1  | Y00433 | 138320 | GEN-TJ  | Human mRNA for glutathione peroxidase (EC 1.11.1.9.)                       | 1110 | 792A>C  | 3     |
| GPX3  | X58295 | 138321 | GEN-38S | Human GPx-3 mRNA for plasma glutathione peroxidase                         | 821  | 773C>T  | 3     |
| GPX3  | X58295 | 138321 | GEN-38S | Human GPx-3 mRNA for plasma glutathione peroxidase                         | 979  | 931G>A  | 3     |
| GPX3  | X58295 | 138321 | GEN-38S | Human GPx-3 mRNA for plasma glutathione peroxidase                         | 1187 | 1139T>G | 3     |
| GPX3  | X58295 | 138321 | GEN-38S | Human GPx-3 mRNA for plasma glutathione peroxidase                         | 1354 | 1306C>T | 3     |
| GPX3  | X58295 | 138321 | GEN-38S | Human GPx-3 mRNA for plasma glutathione peroxidase                         | 1443 | 1395C>T | 3     |
| GPX3  | X58295 | 138321 | GEN-38S | Human GPx-3 mRNA for plasma glutathione peroxidase                         | 1516 | 1468C>A | 3     |
| GPX3  | X58295 | 138321 | GEN-38S | Human GPx-3 mRNA for plasma glutathione peroxidase                         | 1581 | 1533C>T | 3     |
| GPX4  | X71973 | 138322 | GEN-3L1 | H.sapiens GPx-4 mRNA for phospholipid hydroperoxide glutathione peroxidase | 718  | 638T>C  | 3     |
| GPX4  | X71973 | 138322 | GEN-3L1 | H.sapiens GPx-4 mRNA for phospholipid hydroperoxide glutathione peroxidase | 837  | 757C>A  | 3     |
| GPX4  | X71973 | 138322 | GEN-3L1 | H.sapiens GPx-4 mRNA for phospholipid hydroperoxide glutathione peroxidase | 882  | 802A>C  | 3     |
| GSTM3 | J05459 | 138390 | GEN-170 | Human glutathione transferase M3 (GSTM3) mRNA, complete cds                | 687  | 670G>A  | V224I |
| GSTM5 | L02321 | 138385 | GEN-WO  | Human glutathione S-transferase (GSTM5)                                    | 1406 | 1349T>C | 3     |

|       |        |        |         |                                                                                                          |      |         |       |
|-------|--------|--------|---------|----------------------------------------------------------------------------------------------------------|------|---------|-------|
| GSTP1 | X06547 | 134660 | GEN-19N | mRNA, complete cds<br>Human mRNA for class Pi glutathione S-transferase (GST-Pi; E.C.2.5.1.18)           | 319  | 313A>G  | I105V |
| GSTP1 | X06547 | 134660 | GEN-19N | Human mRNA for class Pi glutathione S-transferase (GST-Pi; E.C.2.5.1.18)                                 | 347  | 341C>T  | A114V |
| GSTP1 | X06547 | 134660 | GEN-19N | Human mRNA for class Pi glutathione S-transferase (GST-Pi; E.C.2.5.1.18)                                 | 561  | 555C>T  | S     |
| GSTT2 | L38503 | 600437 | GEN-2PC | Homo sapiens glutathione S-transferase theta 2 (GSTT2) mRNA, complete cds                                | 203  | 203C>T  | S68L  |
| GSTT2 | L38503 | 600437 | GEN-2PC | Homo sapiens glutathione S-transferase theta 2 (GSTT2) mRNA, complete cds                                | 543  | 543C>T  | S     |
| HADHA | U04627 | 600890 | GEN-155 | Human 78 kDa gastrin-binding protein mRNA, complete cds                                                  | 1507 | 1507G>A | V503M |
| HADHB | D16481 | 143450 | GEN-1Y5 | Human mRNA for mitochondrial 3-ketoacyl-CoA thiolase beta-subunit of trifunctional protein, complete cds | 871  | 825T>C  | S     |
| HADHB | D16481 | 143450 | GEN-1Y5 | Human mRNA for mitochondrial 3-ketoacyl-CoA thiolase beta-subunit of trifunctional protein, complete cds | 1607 | 1561G>C | 3     |
| HADHB | D16481 | 143450 | GEN-1Y5 | Human mRNA for mitochondrial 3-ketoacyl-CoA thiolase beta-subunit of trifunctional protein, complete cds | 1908 | 1862A>C | 3     |
| HADHB | D16481 | 143450 | GEN-1Y5 | Human mRNA for mitochondrial 3-ketoacyl-CoA thiolase beta-subunit of trifunctional protein, complete cds | 1911 | 1865A>C | 3     |

|        |          |        |         |                                                                           |      |                |       |
|--------|----------|--------|---------|---------------------------------------------------------------------------|------|----------------|-------|
| HRH1   | AF026261 | 600167 | GEN-26W | Histamine receptor H1                                                     | 1068 | 1068A>G        | S     |
| HSST   | U17970   | 600853 | GEN-20V | Human heparan sulfate N-deacetylase/N-sulfotransferase mRNA, complete cds | 2294 | 2066G>C        | G689A |
| IDS    | L40586   | 309900 | GEN-2SB | Homo sapiens iduronate-2-sulphatase (IDS) mRNA, complete cds              | 565  | 438C>T         | S     |
| J03459 | J03459   | 151570 | GEN-8   | Leukotriene A4 hydrolase                                                  | 140  | 72G>T          | S     |
| J03459 | J03459   | 151570 | GEN-8   | Leukotriene A4 hydrolase                                                  | 1511 | 1443A>T        | E481D |
| J03548 | J03548   | 103260 | GEN-11M | Human adrenodoxin mRNA, complete cds                                      | 1099 | 967G>A         | 3     |
| J03548 | J03548   | 103260 | GEN-11M | Human adrenodoxin mRNA, complete cds                                      | 1123 | 991T>C         | 3     |
| J03548 | J03548   | 103260 | GEN-11M | Human adrenodoxin mRNA, complete cds                                      | 1222 | 1090G>C        | 3     |
| J03548 | J03548   | 103260 | GEN-11M | Human adrenodoxin mRNA, complete cds                                      | 1254 | 1122G>A        | 3     |
| J03571 | J03571   | 152390 | GEN-9   | Lipoxygenases: 5-lipoxygenase (leukocytes)                                | 55   | 21C>T          | S     |
| J03571 | J03571   | 152390 | GEN-9   | Lipoxygenases: 5-lipoxygenase (leukocytes)                                | 304  | 270G>A         | S     |
| J03571 | J03571   | 152390 | GEN-9   | Lipoxygenases: 5-lipoxygenase (leukocytes)                                | 304  | 270G>A         | S     |
| J03571 | J03571   | 152390 | GEN-9   | Lipoxygenases: 5-lipoxygenase (leukocytes)                                | 959  | 925C>A         | P309T |
| J03571 | J03571   | 152390 | GEN-9   | Lipoxygenases: 5-lipoxygenase (leukocytes)                                | 1762 | 1728A>T        | S     |
| J03571 | J03571   | 152390 | GEN-9   | Lipoxygenases: 5-lipoxygenase (leukocytes)                                | 2076 | 2042-2043AC>AC | 3     |
| J03571 | J03571   | 152390 | GEN-9   | Lipoxygenases: 5-lipoxygenase (leukocytes)                                | 2076 | 2042-2043delAC | F     |
| J03571 | J03571   | 152390 | GEN-9   | Lipoxygenases: 5-lipoxygenase (leukocytes)                                | 2328 | 2294C>T        | 3     |
| J03571 | J03571   | 152390 | GEN-9   | Lipoxygenases: 5-lipoxygenase (leukocytes)                                | 2376 | 2342T>G        | 3     |
| J03746 | J03746   | 138330 | GEN-11Z | Human glutathione S-transferase mRNA, complete cds                        | 560  | 487A>G         | 3     |
| J03746 | J03746   | 138330 | GEN-    | Human glutathione S-transferase mRNA, complete cds                        | 598  | 525T>G         | 3     |

| 11Z    |        |        |        |                                                             |                                |      |         |       |  |  |
|--------|--------|--------|--------|-------------------------------------------------------------|--------------------------------|------|---------|-------|--|--|
| J03817 | J03817 | 138350 | GEN-9D | Glutathione S-transferase M1                                | transferrin mRNA, complete cds | 99   | 84T>C   | S     |  |  |
| J03817 | J03817 | 138350 | GEN-9D | Glutathione S-transferase M1                                |                                | 543  | 528C>T  | S     |  |  |
| J03817 | J03817 | 138350 | GEN-9D | Glutathione S-transferase M1                                |                                | 643  | 628T>A  | S210T |  |  |
| J03817 | J03817 | 138350 | GEN-9D | Glutathione S-transferase M1                                |                                | 728  | 713C>G  | 3     |  |  |
| J03817 | J03817 | 138350 | GEN-9D | Glutathione S-transferase M1                                |                                | 902  | 887C>T  | 3     |  |  |
| J04031 | J04031 | 172460 | GEN-CB | Methenyltetrahydrofolate cyclohydrolase                     |                                | 454  | 401G>A  | R134K |  |  |
| J04031 | J04031 | 172460 | GEN-CB | Methenyltetrahydrofolate cyclohydrolase                     |                                | 969  | 916C>G  | Q306E |  |  |
| J04031 | J04031 | 172460 | GEN-CB | Methenyltetrahydrofolate cyclohydrolase                     |                                | 1614 | 1561T>C | S     |  |  |
| J04031 | J04031 | 172460 | GEN-CB | Methenyltetrahydrofolate cyclohydrolase                     |                                | 2011 | 1958G>A | R653Q |  |  |
| J04031 | J04031 | 172460 | GEN-CB | Methenyltetrahydrofolate cyclohydrolase                     |                                | 2335 | 2282C>T | T761M |  |  |
| J04794 | J04794 | None   | GEN-PR | Human aldehyde reductase mRNA, complete cds                 |                                | 661  | 601C>A  | Q201K |  |  |
| J05176 | J05176 | 107280 | GEN-PT | Human alpha-1-antichymotrypsin mRNA, 3' end                 |                                | 240  | 240A>G  | S     |  |  |
| J05176 | J05176 | 107280 | GEN-PT | Human alpha-1-antichymotrypsin mRNA, 3' end                 |                                | 327  | 327C>T  | S     |  |  |
| J05176 | J05176 | 107280 | GEN-PT | Human alpha-1-antichymotrypsin mRNA, 3' end                 |                                | 554  | 554T>C  | V185A |  |  |
| K03001 | K03001 | 100650 | GEN-5N | Aldehyde dehydrogenase 2, mitochondrial                     |                                | 656  | 656T>A  | V219E |  |  |
| K03001 | K03001 | 100650 | GEN-5N | Aldehyde dehydrogenase 2, mitochondrial                     |                                | 988  | 988G>C  | V330L |  |  |
| K03191 | K03191 | 108330 | GEN-9E | Cytochrome P450, subfamily I (aromatic compound-inducible), |                                | 1470 | 1384G>A | V462I |  |  |

|        |        |        |         |                                                                                               |      |         |        |
|--------|--------|--------|---------|-----------------------------------------------------------------------------------------------|------|---------|--------|
| L02932 | L02932 | 170998 | GEN-KW4 | polypeptide 1<br>Human peroxisome<br>proliferator activated<br>receptor mRNA, complete<br>cds | 648  | 432G>A  | S      |
| L04751 | L04751 | 601310 | GEN-157 | Human cytochrome p-450<br>4A (CYP4A) mRNA,<br>complete cds                                    | 1001 | 969C>T  | S      |
| L04751 | L04751 | 601310 | GEN-157 | Human cytochrome p-450<br>4A (CYP4A) mRNA,<br>complete cds                                    | 1333 | 1301T>C | F434S  |
| L04751 | L04751 | 601310 | GEN-157 | Human cytochrome p-450<br>4A (CYP4A) mRNA,<br>complete cds                                    | 1406 | 1374T>C | S      |
| L04751 | L04751 | 601310 | GEN-157 | Human cytochrome p-450<br>4A (CYP4A) mRNA,<br>complete cds                                    | 1944 | 1912A>G | 3      |
| L04751 | L04751 | 601310 | GEN-157 | Human cytochrome p-450<br>4A (CYP4A) mRNA,<br>complete cds                                    | 1970 | 1938G>A | 3      |
| L04751 | L04751 | 601310 | GEN-157 | Human cytochrome p-450<br>4A (CYP4A) mRNA,<br>complete cds                                    | 2011 | 1979C>T | 3      |
| L04751 | L04751 | 601310 | GEN-157 | Human cytochrome p-450<br>4A (CYP4A) mRNA,<br>complete cds                                    | 2047 | 2015T>C | 3      |
| L04751 | L04751 | 601310 | GEN-157 | Human cytochrome p-450<br>4A (CYP4A) mRNA,<br>complete cds                                    | 2115 | 2083A>G | 3      |
| L05628 | L05628 | 158343 | GEN-4D9 | Human multidrug<br>resistance-associated<br>protein (MRP) mRNA,<br>complete cds               | 3369 | 3173G>A | R1058Q |
| L05628 | L05628 | 158343 | GEN-4D9 | Human multidrug<br>resistance-associated<br>protein (MRP) mRNA,<br>complete cds               | 4198 | 4002G>A | S      |
| L10819 | L10819 | 171150 | GEN-LVD | Homo sapiens aryl<br>sulfotransferase mRNA,<br>complete cds                                   | 191  | 153C>T  | S      |
| L10819 | L10819 | 171150 | GEN-    | Homo sapiens aryl<br>complete cds                                                             | 200  | 162G>A  | S      |

|        |        |        |             |                                                                                                                                                                            |      |         |       |
|--------|--------|--------|-------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------|---------|-------|
| L10819 | L10819 | 171150 | LVD         | sulfotransferase mRNA,<br>complete cds                                                                                                                                     | 230  | 192T>C  | S     |
| L10819 | L10819 | 171150 | GEN-<br>LVD | Homo sapiens aryl<br>sulfotransferase mRNA,<br>complete cds                                                                                                                | 242  | 204G>A  | S     |
| L10819 | L10819 | 171150 | GEN-<br>LVD | Homo sapiens aryl<br>sulfotransferase mRNA,<br>complete cds                                                                                                                | 295  | 257C>T  | A86V  |
| L10819 | L10819 | 171150 | GEN-<br>LVD | Homo sapiens aryl<br>sulfotransferase mRNA,<br>complete cds                                                                                                                | 330  | 292G>A  | D98N  |
| L10819 | L10819 | 171150 | GEN-<br>LVD | Homo sapiens aryl<br>sulfotransferase mRNA,<br>complete cds                                                                                                                | 338  | 300G>A  | S     |
| L10819 | L10819 | 171150 | GEN-<br>LVD | Homo sapiens aryl<br>sulfotransferase mRNA,<br>complete cds                                                                                                                | 638  | 600C>G  | S     |
| L10819 | L10819 | 171150 | GEN-<br>LVD | Homo sapiens aryl<br>sulfotransferase mRNA,<br>complete cds                                                                                                                | 676  | 638A>G  | H213R |
| L10819 | L10819 | 171150 | GEN-<br>LVD | Homo sapiens aryl<br>sulfotransferase mRNA,<br>complete cds                                                                                                                | 940  | 902G>A  | 3     |
| L10819 | L10819 | 171150 | GEN-<br>LVD | Homo sapiens aryl<br>sulfotransferase mRNA,<br>complete cds                                                                                                                | 1011 | 973T>C  | 3     |
| L11696 | L11696 | 104614 | GEN-D6      | Solute carrier family 3<br>(cystine, dibasic and<br>neutral amino acid<br>transporters, activator of<br>cystine, dibasic and neutral<br>amino acid transport),<br>member 1 | 1897 | 1854G>A | M618I |
| L11696 | L11696 | 104614 | GEN-D6      | Solute carrier family 3<br>(cystine, dibasic and<br>neutral amino acid<br>transporters, activator of<br>cystine, dibasic and neutral<br>amino acid transport),<br>member 1 | 2232 | 2189T>C | 3     |

|        |        |        |         |                                                                                |      |                |       |
|--------|--------|--------|---------|--------------------------------------------------------------------------------|------|----------------|-------|
| L13286 | L13286 | 600125 | GEN-103 | Human mitochondrial 1,25-dihydroxyvitamin D3 24-hydroxylase mRNA, complete cds | 2031 | 1638G>A        | 3     |
| L19956 | L19956 | 600641 | GEN-LVE | Human aryl sulfotransferase mRNA, complete cds                                 | 243  | 105A>G         | S     |
| L19956 | L19956 | 600641 | GEN-LVE | Human aryl sulfotransferase mRNA, complete cds                                 | 284  | 146C>T         | S49F  |
| L31801 | L31801 | 600682 | GEN-DQ  | Solute carrier family 16 (monocarboxylic acid transporters), member 1          | 1482 | 1470A>T        | E490D |
| L31801 | L31801 | 600682 | GEN-DQ  | Solute carrier family 16 (monocarboxylic acid transporters), member 1          | 1772 | 1760G>C        | 3     |
| L32179 | L32179 | 600338 | GEN-2IW | Human arylacetamide deacetylase mRNA, complete cds                             | 1366 | 1281G>A        | 3     |
| L78207 | L78207 | 600509 | GEN-5Q  | Cell surface receptor for sulfonyleureas on pancreatic b cells                 | 4019 | 3981A>G        | S     |
| LCT    | X07994 | 603202 | GEN-1F6 | Human mRNA for lactase-phlorizin hydrolase LPH (EC 3.2.1.23-62)                | 5845 | 5834C>G        | 3     |
| LIPC   | J03540 | 151670 | GEN-11J | Human hepatic lipase mRNA, complete cds                                        | 469  | 465T>G         | S     |
| LIPC   | J03540 | 151670 | GEN-11J | Human hepatic lipase mRNA, complete cds                                        | 595  | 591A>G         | S     |
| LIPC   | J03540 | 151670 | GEN-11J | Human hepatic lipase mRNA, complete cds                                        | 648  | 644G>A         | S215N |
| LIPC   | J03540 | 151670 | GEN-11J | Human hepatic lipase mRNA, complete cds                                        | 817  | 813C>T         | S     |
| LIPC   | J03540 | 151670 | GEN-11J | Human hepatic lipase mRNA, complete cds                                        | 1441 | 1437C>A        | S     |
| M10901 | M10901 | 138040 | GEN-2W  | Corticosteroid nuclear receptor b                                              | 1220 | 1088A>G        | N363S |
| M10901 | M10901 | 138040 | GEN-2W  | Corticosteroid nuclear receptor b                                              | 2024 | 1892-1893AG>AG | S     |

|        |        |        |         |                                                                  |      |                |       |
|--------|--------|--------|---------|------------------------------------------------------------------|------|----------------|-------|
| M10901 | M10901 | 138040 | GEN-2W  | Corticosteroid nuclear receptor b                                | 2024 | 1892-1893delAG | F     |
| M10901 | M10901 | 138040 | GEN-2W  | Corticosteroid nuclear receptor b                                | 2054 | 1922A>T        | D641V |
| M10901 | M10901 | 138040 | GEN-2W  | Corticosteroid nuclear receptor b                                | 2372 | 2240T>G        | I747S |
| M10901 | M10901 | 138040 | GEN-2W  | Corticosteroid nuclear receptor b                                | 2391 | 2259A>C        | L753F |
| M10901 | M10901 | 138040 | GEN-2W  | Corticosteroid nuclear receptor b                                | 2391 | 2259A>T        | L753F |
| M11050 | M11050 | 138040 | GEN-7Y  | Glucocorticoid receptor                                          | 2166 | 2034C>T        | S     |
| M11050 | M11050 | 138040 | GEN-7Y  | Glucocorticoid receptor                                          | 3353 | 3221T>G        | 3     |
| M11050 | M11050 | 138040 | GEN-7Y  | Glucocorticoid receptor                                          | 3398 | 3266T>G        | 3     |
| M14565 | M14565 | 118485 | GEN-30  | Cytochrome P450, subfamily XIA (cholesterol side chain cleavage) | 947  | 903G>C         | M301I |
| M14758 | M14758 | 171050 | GEN-1S6 | P glycoprotein 1                                                 | 978  | 554-555TT>GA>G | V185G |
| M14758 | M14758 | 171050 | GEN-1S6 | P glycoprotein 1                                                 | 978  | 554-555TT>TT   | S     |
| M14758 | M14758 | 171050 | GEN-1S6 | P glycoprotein 1                                                 | 1623 | 1199G>A        | S400N |
| M14758 | M14758 | 171050 | GEN-1S6 | P glycoprotein 1                                                 | 3101 | 2677G>A        | A893T |
| M14758 | M14758 | 171050 | GEN-1S6 | P glycoprotein 1                                                 | 3101 | 2677G>T        | A893S |
| M14758 | M14758 | 171050 | GEN-1S6 | P glycoprotein 1                                                 | 3859 | 3435C>T        | S     |
| M14758 | M14758 | 171050 | GEN-1S6 | P glycoprotein 1                                                 | 4460 | 4036A>G        | 3     |
| M15856 | M15856 | 238600 | GEN-33  | Lipoprotein lipase                                               | 136  | (-39)T>C       | 5     |
| M15856 | M15856 | 238600 | GEN-33  | Lipoprotein lipase                                               | 280  | 106G>A         | D36N  |
| M15856 | M15856 | 238600 | GEN-33  | Lipoprotein lipase                                               | 438  | 264T>A         | F     |
| M15856 | M15856 | 238600 | GEN-33  | Lipoprotein lipase                                               | 447  | 273G>A         | F     |
| M15856 | M15856 | 238600 | GEN-33  | Lipoprotein lipase                                               | 474  | 300C>A         | F     |
| M15856 | M15856 | 238600 | GEN-33  | Lipoprotein lipase                                               | 480  | 306A>C         | R102S |
| M15856 | M15856 | 238600 | GEN-33  | Lipoprotein lipase                                               | 511  | 337T>C         | W113R |
| M15856 | M15856 | 238600 | GEN-33  | Lipoprotein lipase                                               | 571  | 397C>T         | F     |



|        |        |        |        |                                                            |      |          |       |
|--------|--------|--------|--------|------------------------------------------------------------|------|----------|-------|
| M15856 | M15856 | 238600 | GEN-33 | Lipoprotein lipase                                         | 680  | 506G>A   | G169E |
| M15856 | M15856 | 238600 | GEN-33 | Lipoprotein lipase                                         | 722  | 548A>G   | D183G |
| M15856 | M15856 | 238600 | GEN-33 | Lipoprotein lipase                                         | 770  | 596C>G   | S199C |
| M15856 | M15856 | 238600 | GEN-33 | Lipoprotein lipase                                         | 781  | 607G>A   | A203T |
| M15856 | M15856 | 238600 | GEN-33 | Lipoprotein lipase                                         | 795  | 621C>G   | D207E |
| M15856 | M15856 | 238600 | GEN-33 | Lipoprotein lipase                                         | 818  | 644G>A   | G215E |
| M15856 | M15856 | 238600 | GEN-33 | Lipoprotein lipase                                         | 836  | 662T>C   | I221T |
| M15856 | M15856 | 238600 | GEN-33 | Lipoprotein lipase                                         | 839  | 665G>A   | G222E |
| M15856 | M15856 | 238600 | GEN-33 | Lipoprotein lipase                                         | 867  | 693C>G   | D231E |
| M15856 | M15856 | 238600 | GEN-33 | Lipoprotein lipase                                         | 875  | 701C>T   | P234L |
| M15856 | M15856 | 238600 | GEN-33 | Lipoprotein lipase                                         | 916  | 742delG  | F     |
| M15856 | M15856 | 238600 | GEN-33 | Lipoprotein lipase                                         | 983  | 809G>A   | R270H |
| M15856 | M15856 | 238600 | GEN-33 | Lipoprotein lipase                                         | 985  | 811T>A   | S271T |
| M15856 | M15856 | 238600 | GEN-33 | Lipoprotein lipase                                         | 1003 | 829G>A   | D277N |
| M15856 | M15856 | 238600 | GEN-33 | Lipoprotein lipase                                         | 1127 | 953A>G   | N318S |
| M15856 | M15856 | 238600 | GEN-33 | Lipoprotein lipase                                         | 1255 | 1081G>A  | A361T |
| M15856 | M15856 | 238600 | GEN-33 | Lipoprotein lipase                                         | 1348 | 1174C>G  | L392V |
| M15856 | M15856 | 238600 | GEN-33 | Lipoprotein lipase                                         | 1401 | 1227G>A  | F     |
| M15856 | M15856 | 238600 | GEN-33 | Lipoprotein lipase                                         | 1508 | 1334G>A  | C445Y |
| M15856 | M15856 | 238600 | GEN-33 | Lipoprotein lipase                                         | 1595 | 1421C>G  | F     |
| M15856 | M15856 | 238600 | GEN-33 | Lipoprotein lipase                                         | 1973 | 1799T>C  | 3     |
| M15856 | M15856 | 238600 | GEN-33 | Lipoprotein lipase                                         | 2428 | 2254T>A  | 3     |
| M15856 | M15856 | 238600 | GEN-33 | Lipoprotein lipase                                         | 2743 | 2569T>C  | 3     |
| M15856 | M15856 | 238600 | GEN-33 | Lipoprotein lipase                                         | 2851 | 2677A>G  | 3     |
| M15856 | M15856 | 238600 | GEN-33 | Lipoprotein lipase                                         | 2851 | 2677A>G  | 3     |
| M15856 | M15856 | 238600 | GEN-33 | Lipoprotein lipase                                         | 2958 | 2784G>A  | 3     |
| M15856 | M15856 | 238600 | GEN-33 | Lipoprotein lipase                                         | 3017 | 2843T>C  | 3     |
| M15856 | M15856 | 238600 | GEN-33 | Lipoprotein lipase                                         | 3272 | 3098T>C  | 3     |
| M15856 | M15856 | 238600 | GEN-33 | Lipoprotein lipase                                         | 3272 | 3098T>C  | 3     |
| M15856 | M15856 | 238600 | GEN-33 | Lipoprotein lipase                                         | 3343 | 3169T>C  | 3     |
| M15856 | M15856 | 238600 | GEN-33 | Lipoprotein lipase                                         | 3447 | 3273C>T  | 3     |
| M15872 | M15872 | 138360 | GEN-QS | Human glutathione S-transferase 2 (GST) mRNA, complete cds | 16   | (-40)G>A | 5     |
| M15872 | M15872 | 138360 | GEN-QS | Human glutathione S-transferase 2 (GST) mRNA, complete cds | 54   | (-2)T>C  | 5     |

|        |        |        |        |                                         |      |                |       |
|--------|--------|--------|--------|-----------------------------------------|------|----------------|-------|
| M15872 | M15872 | 138360 | GEN-QS | mRNA, complete cds                      | 84   | 29T>C          | F10S  |
|        |        |        |        | Human glutathione S-transferase 2 (GST) |      |                |       |
| M15872 | M15872 | 138360 | GEN-QS | mRNA, complete cds                      | 111  | 56C>T          | T19I  |
|        |        |        |        | Human glutathione S-transferase 2 (GST) |      |                |       |
| M15872 | M15872 | 138360 | GEN-QS | mRNA, complete cds                      | 170  | 115G>T         | F     |
|        |        |        |        | Human glutathione S-transferase 2 (GST) |      |                |       |
| M15872 | M15872 | 138360 | GEN-QS | mRNA, complete cds                      | 321  | 266G>A         | R89K  |
|        |        |        |        | Human glutathione S-transferase 2 (GST) |      |                |       |
| M15872 | M15872 | 138360 | GEN-QS | mRNA, complete cds                      | 376  | 321C>T         | S     |
|        |        |        |        | Human glutathione S-transferase 2 (GST) |      |                |       |
| M15872 | M15872 | 138360 | GEN-QS | mRNA, complete cds                      | 430  | 375G>A         | S     |
|        |        |        |        | Human glutathione S-transferase 2 (GST) |      |                |       |
| M15872 | M15872 | 138360 | GEN-QS | mRNA, complete cds                      | 622  | 567C>T         | S     |
|        |        |        |        | Human glutathione S-transferase 2 (GST) |      |                |       |
| M15872 | M15872 | 138360 | GEN-QS | mRNA, complete cds                      | 684  | 629A>C         | E210A |
|        |        |        |        | Human glutathione S-transferase 2 (GST) |      |                |       |
| M15872 | M15872 | 138360 | GEN-QS | mRNA, complete cds                      | 701  | 646G>T         | A216S |
|        |        |        |        | Human glutathione S-transferase 2 (GST) |      |                |       |
| M16505 | M16505 | 308100 | GEN-7D | mRNA, complete cds                      | 2725 | 2505T>G        | 3     |
|        |        |        |        | STERYL-SULFATASE                        |      |                |       |
| M16505 | M16505 | 308100 | GEN-7D | PRECURSOR                               | 4364 | 4144G>A        | 3     |
|        |        |        |        | STERYL-SULFATASE                        |      |                |       |
| M16505 | M16505 | 308100 | GEN-7D | PRECURSOR                               | 4665 | 4445A>G        | 3     |
|        |        |        |        | STERYL-SULFATASE                        |      |                |       |
| M16505 | M16505 | 308100 | GEN-7D | PRECURSOR                               | 5894 | 5674A>G        | 3     |
|        |        |        |        | STERYL-SULFATASE                        |      |                |       |
| M16541 | M16541 | 177400 | GEN-35 | Butyrylcholinesterase                   | 422  | 293A>G         | D98G  |
| M16541 | M16541 | 177400 | GEN-35 | Butyrylcholinesterase                   | 557  | 428G>A         | G143D |
| M16541 | M16541 | 177400 | GEN-35 | Butyrylcholinesterase                   | 564  | 435-436TT>AG>A | F146V |
|        |        |        |        |                                         |      | G              |       |

|        |        |        |             |                                                                        |      |         |       |
|--------|--------|--------|-------------|------------------------------------------------------------------------|------|---------|-------|
| M16541 | M16541 | 177400 | GEN-35      | Butyrylcholinesterase                                                  | 568  | 439C>T  | F     |
| M16541 | M16541 | 177400 | GEN-35      | Butyrylcholinesterase                                                  | 596  | 467A>G  | Y156C |
| M16541 | M16541 | 177400 | GEN-35      | Butyrylcholinesterase                                                  | 941  | 812C>T  | T271M |
| M16541 | M16541 | 177400 | GEN-35      | Butyrylcholinesterase                                                  | 961  | 832A>C  | T278P |
| M16541 | M16541 | 177400 | GEN-35      | Butyrylcholinesterase                                                  | 978  | 849G>C  | E283D |
| M16541 | M16541 | 177400 | GEN-35      | Butyrylcholinesterase                                                  | 1201 | 1072T>A | L358I |
| M16541 | M16541 | 177400 | GEN-35      | Butyrylcholinesterase                                                  | 1306 | 1177G>A | G393R |
| M16541 | M16541 | 177400 | GEN-35      | Butyrylcholinesterase                                                  | 1382 | 1253G>T | G418V |
| M16541 | M16541 | 177400 | GEN-35      | Butyrylcholinesterase                                                  | 1549 | 1420T>G | F474V |
| M16541 | M16541 | 177400 | GEN-35      | Butyrylcholinesterase                                                  | 1564 | 1435G>T | F     |
| M16541 | M16541 | 177400 | GEN-35      | Butyrylcholinesterase                                                  | 1703 | 1574A>T | E525V |
| M16541 | M16541 | 177400 | GEN-35      | Butyrylcholinesterase                                                  | 1756 | 1627C>T | R543C |
| M16541 | M16541 | 177400 | GEN-35      | Butyrylcholinesterase                                                  | 1828 | 1699G>A | A567T |
| M16541 | M16541 | 177400 | GEN-35      | Butyrylcholinesterase                                                  | 1828 | 1699G>A | A567T |
| M16541 | M16541 | 177400 | GEN-35      | Butyrylcholinesterase                                                  | 2127 | 1998A>G | 3     |
| M16541 | M16541 | 177400 | GEN-35      | Butyrylcholinesterase                                                  | 2127 | 1998A>G | 3     |
| M16827 | M16827 | 201450 | GEN-EI      | Acyl-Coenzyme A<br>dehydrogenase, C-4 to C-<br>12 straight chain       | 1956 | 1938T>C | 3     |
| M20681 | M20681 | 138170 | GEN-<br>23O | Human glucose<br>transporter-like protein-III<br>(GLUT3), complete cds | 1550 | 1308C>T | S     |
| M20681 | M20681 | 138170 | GEN-<br>23O | Human glucose<br>transporter-like protein-III<br>(GLUT3), complete cds | 3179 | 2937T>C | 3     |
| M20681 | M20681 | 138170 | GEN-<br>23O | Human glucose<br>transporter-like protein-III<br>(GLUT3), complete cds | 3238 | 2996C>T | 3     |
| M20681 | M20681 | 138170 | GEN-<br>23O | Human glucose<br>transporter-like protein-III<br>(GLUT3), complete cds | 3356 | 3114T>C | 3     |
| M20681 | M20681 | 138170 | GEN-<br>23O | Human glucose<br>transporter-like protein-III<br>(GLUT3), complete cds | 3378 | 3136T>C | 3     |
| M20681 | M20681 | 138170 | GEN-<br>23O | Human glucose<br>transporter-like protein-III<br>(GLUT3), complete cds | 3524 | 3282C>A | 3     |
| M20681 | M20681 | 138170 | GEN-<br>23O | Human glucose<br>transporter-like protein-III<br>(GLUT3), complete cds | 3572 | 3330G>T | 3     |

|        |        |        |        |                                                                                    |      |         |       |
|--------|--------|--------|--------|------------------------------------------------------------------------------------|------|---------|-------|
| M21054 | M21054 | 172410 | GEN-3B | (GLUT3), complete cds<br>Phospholipase A-2 (PLA-2)<br>lung                         | 331  | 294G>A  | S     |
| M21054 | M21054 | 172410 | GEN-3B | Phospholipase A-2 (PLA-2)<br>lung                                                  | 400  | 363C>A  | D121E |
| M24400 | M24400 | 118890 | GEN-R2 | Human chymotrypsinogen<br>mRNA, complete cds                                       | 121  | 105G>A  | S     |
| M24400 | M24400 | 118890 | GEN-R2 | Human chymotrypsinogen<br>mRNA, complete cds                                       | 231  | 215C>A  | T72N  |
| M24400 | M24400 | 118890 | GEN-R2 | Human chymotrypsinogen<br>mRNA, complete cds                                       | 460  | 444C>T  | S     |
| M24400 | M24400 | 118890 | GEN-R2 | Human chymotrypsinogen<br>mRNA, complete cds                                       | 649  | 633C>T  | S     |
| M24857 | M24857 | 180190 | GEN-80 | Human chymotrypsinogen<br>mRNA, complete cds<br>Retinoic acid receptor,<br>gamma 1 | 1694 | 1280C>T | S427L |
| M24895 | M24895 | 104660 | GEN-R3 | Homo sapiens alpha-<br>amylase mRNA, complete<br>cds                               | 193  | 147C>G  | S     |
| M24895 | M24895 | 104660 | GEN-R3 | Homo sapiens alpha-<br>amylase mRNA, complete<br>cds                               | 967  | 921A>G  | S     |
| M24895 | M24895 | 104660 | GEN-R3 | Homo sapiens alpha-<br>amylase mRNA, complete<br>cds                               | 1009 | 963G>C  | S     |
| M24895 | M24895 | 104660 | GEN-R3 | Homo sapiens alpha-<br>amylase mRNA, complete<br>cds                               | 1027 | 981T>A  | S     |
| M24895 | M24895 | 104660 | GEN-R3 | Homo sapiens alpha-<br>amylase mRNA, complete<br>cds                               | 1054 | 1008T>C | S     |
| M24895 | M24895 | 104660 | GEN-R3 | Homo sapiens alpha-<br>amylase mRNA, complete<br>cds                               | 1093 | 1047T>A | S     |
| M24895 | M24895 | 104660 | GEN-R3 | Homo sapiens alpha-<br>amylase mRNA, complete<br>cds                               | 1178 | 1132A>G | N378D |
| M24895 | M24895 | 104660 | GEN-R3 | Homo sapiens alpha-<br>amylase mRNA, complete<br>cds                               | 1191 | 1145T>C | I382T |
| M24895 | M24895 | 104660 | GEN-R3 | Homo sapiens alpha-<br>amylase mRNA, complete<br>cds                               | 1394 | 1348A>T | T450S |

|        |        |        |        |                                                                                  |      |         |      |
|--------|--------|--------|--------|----------------------------------------------------------------------------------|------|---------|------|
| M24895 | M24895 | 104660 | GEN-R3 | cds<br>Homo sapiens alpha-<br>amylase mRNA, complete                             | 1474 | 1428T>C | S    |
| M24895 | M24895 | 104660 | GEN-R3 | cds<br>Homo sapiens alpha-<br>amylase mRNA, complete                             | 1492 | 1446C>T | S    |
| M24895 | M24895 | 104660 | GEN-R3 | cds<br>Homo sapiens alpha-<br>amylase mRNA, complete                             | 1504 | 1458C>T | S    |
| M24895 | M24895 | 104660 | GEN-R3 | cds<br>Homo sapiens alpha-<br>amylase mRNA, complete                             | 1543 | 1497G>A | S    |
| M24895 | M24895 | 104660 | GEN-R3 | cds<br>Homo sapiens alpha-<br>amylase mRNA, complete                             | 1579 | 1533A>G | S    |
| M24895 | M24895 | 104660 | GEN-R3 | cds<br>Homo sapiens alpha-<br>amylase mRNA, complete                             | 1601 | 1555T>A | 3    |
| M26393 | M26393 | 201470 | GEN-EW | cds<br>Acyl-Coenzyme A<br>dehydrogenase, C-2 to C-3<br>short chain               | 1797 | 1765A>G | 3    |
| M29874 | M29874 | None   | GEN-3I | Cytochrome P450,<br>subfamily IIB<br>(phenobarbital-inducible),<br>polypeptide 6 | 2758 | 2752T>A | 3    |
| M29874 | M29874 | None   | GEN-3I | Cytochrome P450,<br>subfamily IIB<br>(phenobarbital-inducible),<br>polypeptide 6 | 2836 | 2830G>A | 3    |
| M29874 | M29874 | None   | GEN-3I | Cytochrome P450,<br>subfamily IIB<br>(phenobarbital-inducible),<br>polypeptide 6 | 2902 | 2896T>C | 3    |
| M29882 | M29882 | 107670 | GEN-6R | polypeptide 6<br>Apolipoprotein A-II                                             | 26   | 17C>A   | A6E  |
| M29882 | M29882 | 107670 | GEN-6R | Apolipoprotein A-II                                                              | 183  | 174G>A  | S    |
| M29882 | M29882 | 107670 | GEN-6R | Apolipoprotein A-II                                                              | 192  | 183C>A  | S    |
| M34479 | M34479 | 179060 | GEN-F9 | Pyruvate dehydrogenase<br>(lipoamide) beta                                       | 109  | 109G>A  | D37N |
| M34479 | M34479 | 179060 | GEN-F9 | Pyruvate dehydrogenase<br>(lipoamide) beta                                       | 438  | 438A>G  | S    |

|        |        |        |         |                                                                          |      |         |       |
|--------|--------|--------|---------|--------------------------------------------------------------------------|------|---------|-------|
| M34479 | M34479 | 179060 | GEN-F9  | Pyruvate dehydrogenase (lipoamide) beta                                  | 1172 | 1172A>C | 3     |
| M34479 | M34479 | 179060 | GEN-F9  | Pyruvate dehydrogenase (lipoamide) beta                                  | 1179 | 1179C>T | 3     |
| M34479 | M34479 | 179060 | GEN-F9  | Pyruvate dehydrogenase (lipoamide) beta                                  | 1323 | 1323C>A | 3     |
| M34479 | M34479 | 179060 | GEN-F9  | Pyruvate dehydrogenase (lipoamide) beta                                  | 1376 | 1376G>C | 3     |
| M34479 | M34479 | 179060 | GEN-F9  | Pyruvate dehydrogenase (lipoamide) beta                                  | 1433 | 1433C>T | 3     |
| M55040 | M55040 | 100740 | GEN-3Q  | acetylcholinesterase                                                     | 323  | 167C>T  | P56L  |
| M55040 | M55040 | 100740 | GEN-3Q  | acetylcholinesterase                                                     | 1154 | 998T>A  | V333E |
| M55040 | M55040 | 100740 | GEN-3Q  | acetylcholinesterase                                                     | 1213 | 1057C>A | H353N |
| M55040 | M55040 | 100740 | GEN-3Q  | acetylcholinesterase                                                     | 1482 | 1326G>T | S     |
| M55040 | M55040 | 100740 | GEN-3Q  | acetylcholinesterase                                                     | 1587 | 1431C>T | S     |
| M55040 | M55040 | 100740 | GEN-3Q  | acetylcholinesterase                                                     | 1587 | 1431C>T | S     |
| M55040 | M55040 | 100740 | GEN-3Q  | acetylcholinesterase                                                     | 1663 | 1507T>C | F503L |
| M55531 | M55531 | 138230 | GEN-FF  | Solute carrier family 2 (facilitated glucose transporter), member 5      | 1208 | 1133T>G | V378G |
| M55531 | M55531 | 138230 | GEN-FF  | Solute carrier family 2 (facilitated glucose transporter), member 5      | 1975 | 1900C>T | 3     |
| M55531 | M55531 | 138230 | GEN-FF  | Solute carrier family 2 (facilitated glucose transporter), member 5      | 1985 | 1910A>G | 3     |
| M57899 | M57899 | 191740 | GEN-38A | Human bilirubin UDP-glucuronosyltransferase isozyme 1 mRNA, complete cds | 1828 | 1813C>T | 3     |
| M57899 | M57899 | 191740 | GEN-38A | Human bilirubin UDP-glucuronosyltransferase isozyme 1 mRNA, complete cds | 1956 | 1941C>G | 3     |
| M57899 | M57899 | 191740 | GEN-38A | Human bilirubin UDP-glucuronosyltransferase isozyme 1 mRNA, complete cds | 2057 | 2042C>G | 3     |
| M58525 | M58525 | 116790 | GEN-3S  | Catechol-O-methyltransferase                                             | 390  | 186T>C  | S     |

|        |        |        |        |                                         |      |         |       |
|--------|--------|--------|--------|-----------------------------------------|------|---------|-------|
| M58525 | M58525 | 116790 | GEN-3S | Catechol-O-methyltransferase            | 390  | 186T>C  | S     |
| M58525 | M58525 | 116790 | GEN-3S | Catechol-O-methyltransferase            | 418  | 214G>T  | A72S  |
| M58525 | M58525 | 116790 | GEN-3S | Catechol-O-methyltransferase            | 423  | 219G>A  | S     |
| M58525 | M58525 | 116790 | GEN-3S | Catechol-O-methyltransferase            | 612  | 408C>G  | S     |
| M58525 | M58525 | 116790 | GEN-3S | Catechol-O-methyltransferase            | 676  | 472A>G  | M158V |
| M58525 | M58525 | 116790 | GEN-3S | Catechol-O-methyltransferase            | 676  | 472A>G  | M158V |
| M58525 | M58525 | 116790 | GEN-3S | Catechol-O-methyltransferase            | 813  | 609C>T  | S     |
| M58525 | M58525 | 116790 | GEN-3S | Catechol-O-methyltransferase            | 1031 | 827delC | F     |
| M58525 | M58525 | 116790 | GEN-3S | Catechol-O-methyltransferase            | 1039 | 835C>A  | 3     |
| M60761 | M60761 | 156569 | GEN-FL | O-6-methylguanine-DNA methyltransferase | 174  | 159C>T  | S     |
| M60761 | M60761 | 156569 | GEN-FL | O-6-methylguanine-DNA methyltransferase | 174  | 159C>T  | S     |
| M60761 | M60761 | 156569 | GEN-FL | O-6-methylguanine-DNA methyltransferase | 174  | 159C>T  | S     |
| M60761 | M60761 | 156569 | GEN-FL | O-6-methylguanine-DNA methyltransferase | 210  | 195G>C  | W65C  |
| M60761 | M60761 | 156569 | GEN-FL | O-6-methylguanine-DNA methyltransferase | 264  | 249A>T  | S     |
| M60761 | M60761 | 156569 | GEN-FL | O-6-methylguanine-DNA methyltransferase | 265  | 250C>T  | L84F  |
| M60761 | M60761 | 156569 | GEN-FL | O-6-methylguanine-DNA methyltransferase | 265  | 250C>T  | L84F  |
| M60761 | M60761 | 156569 | GEN-FL | O-6-methylguanine-DNA methyltransferase | 442  | 427A>G  | I143V |
| M60761 | M60761 | 156569 | GEN-FL | O-6-methylguanine-DNA methyltransferase | 442  | 427A>G  | I143V |
| M60761 | M60761 | 156569 | GEN-FL | O-6-methylguanine-DNA methyltransferase | 493  | 478G>A  | G160R |
| M60761 | M60761 | 156569 | GEN-FL | O-6-methylguanine-DNA methyltransferase | 548  | 533A>G  | K178R |
| M60761 | M60761 | 156569 | GEN-FL | O-6-methylguanine-DNA methyltransferase | 582  | 567G>A  | S     |

|        |        |        |         |                                                                            |      |         |       |
|--------|--------|--------|---------|----------------------------------------------------------------------------|------|---------|-------|
| M61855 | M61855 | 601130 | GEN-3C1 | methytransferase<br>Human cytochrome<br>P450C9 (CYP2C9)<br>mRNA, clone 25  | 852  | 853T>A  | 3     |
| M61855 | M61855 | 601130 | GEN-3C1 | Human cytochrome<br>P450C9 (CYP2C9)<br>mRNA, clone 25                      | 1085 | 1086A>G | 3     |
| M61855 | M61855 | 601130 | GEN-3C1 | Human cytochrome<br>P450C9 (CYP2C9)<br>mRNA, clone 25                      | 1437 | 1438T>A | 3     |
| M63012 | M63012 | 168820 | GEN-9F  | Paraoxonase 1                                                              | 172  | 163A>T  | M55L  |
| M63509 | M63509 | 138380 | GEN-9G  | Glutathione S-transferase<br>M2 (muscle)                                   | 644  | 628A>T  | T210S |
| M64082 | M64082 | 136130 | GEN-9H  | Flavin-containing<br>monooxygenase 1<br>(DIMETHYLANILINE<br>MONOOXYGENASE) | 1286 | 1188A>G | S     |
| M64082 | M64082 | 136130 | GEN-9H  | Flavin-containing<br>monooxygenase 1<br>(DIMETHYLANILINE<br>MONOOXYGENASE) | 1808 | 1710C>T | 3     |
| M64082 | M64082 | 136130 | GEN-9H  | Flavin-containing<br>monooxygenase 1<br>(DIMETHYLANILINE<br>MONOOXYGENASE) | 1904 | 1806C>T | 3     |
| M64592 | M64592 | 120420 | GEN-3X  | Granulocyte colony-<br>stimulating factor                                  | 271  | 271T>G  | Y91D  |
| M64592 | M64592 | 120420 | GEN-3X  | Granulocyte colony-<br>stimulating factor                                  | 1533 | 1533C>T | S     |
| M64799 | M64799 | None   | GEN-4DN | Histamine receptor H2                                                      | 398  | 398T>C  | V133A |
| M64799 | M64799 | None   | GEN-4DN | Histamine receptor H2                                                      | 525  | 525A>T  | K175N |
| M64799 | M64799 | None   | GEN-4DN | Histamine receptor H2                                                      | 620  | 620A>G  | K207R |
| M64799 | M64799 | None   | GEN-4DN | Histamine receptor H2                                                      | 649  | 649A>G  | N217D |
| M64799 | M64799 | None   | GEN-4DN | Histamine receptor H2                                                      | 692  | 692A>G  | K231R |
| M64799 | M64799 | None   | GEN-4DN | Histamine receptor H2                                                      | 802  | 802G>A  | V268M |



|        |        |        |         |                                                                            |      |           |       |
|--------|--------|--------|---------|----------------------------------------------------------------------------|------|-----------|-------|
| M68867 | M68867 | 180231 | GEN-S1  | Human cellular retinoic acid-binding protein II (CRABP) mRNA, complete cds | 604  | 506C>A    | 3     |
| M68895 | M68895 | 103735 | GEN-MH7 | Human alcohol dehydrogenase 6 gene, complete cds                           | 547  | 454G>A    | V152M |
| M69226 | M69226 | 309850 | GEN-3Z  | Monoamine oxidase A                                                        | 435  | 385A>C    | S     |
| M69226 | M69226 | 309850 | GEN-3Z  | Monoamine oxidase A                                                        | 936  | 886C>T    | F     |
| M69226 | M69226 | 309850 | GEN-3Z  | Monoamine oxidase A                                                        | 941  | 891T>G    | S     |
| M69226 | M69226 | 309850 | GEN-3Z  | Monoamine oxidase A                                                        | 941  | 891T>G    | S     |
| M69226 | M69226 | 309850 | GEN-3Z  | Monoamine oxidase A                                                        | 1076 | 1026A>T   | S     |
| M69226 | M69226 | 309850 | GEN-3Z  | Monoamine oxidase A                                                        | 1373 | 1323G>A   | F     |
| M69226 | M69226 | 309850 | GEN-3Z  | Monoamine oxidase A                                                        | 1460 | 1410C>T   | S     |
| M69226 | M69226 | 309850 | GEN-3Z  | Monoamine oxidase A                                                        | 1460 | 1410C>T   | S     |
| M69226 | M69226 | 309850 | GEN-3Z  | Monoamine oxidase A                                                        | 1609 | 1559A>G   | K520R |
| M80244 | M80244 | 600182 | GEN-3UJ | Human E16 mRNA, complete cds                                               | 202  | (-109)G>C | 5     |
| M80244 | M80244 | 600182 | GEN-3UJ | Human E16 mRNA, complete cds                                               | 520  | 210T>C    | S     |
| M80244 | M80244 | 600182 | GEN-3UJ | Human E16 mRNA, complete cds                                               | 1185 | 875G>A    | 3     |
| M80244 | M80244 | 600182 | GEN-3UJ | Human E16 mRNA, complete cds                                               | 1473 | 1163C>G   | 3     |
| M80244 | M80244 | 600182 | GEN-3UJ | Human E16 mRNA, complete cds                                               | 1692 | 1382C>T   | 3     |
| M80244 | M80244 | 600182 | GEN-3UJ | Human E16 mRNA, complete cds                                               | 2591 | 2281A>G   | 3     |
| M80244 | M80244 | 600182 | GEN-3UJ | Human E16 mRNA, complete cds                                               | 3138 | 2828G>C   | 3     |
| M80244 | M80244 | 600182 | GEN-3UJ | Human E16 mRNA, complete cds                                               | 3538 | 3228T>C   | 3     |
| M96234 | M96234 | 138333 | GEN-9J  | Glutathione S-transferase M4                                               | 797  | 534T>C    | S     |
| M98045 | M98045 | 136510 | GEN-4C3 | Homo sapiens folypolyglutamate synthetase mRNA, complete cds               | 802  | 732C>T    | S     |
| M98045 | M98045 | 136510 | GEN-4C3 | Homo sapiens folypolyglutamate                                             | 1747 | 1677G>T   | 3     |

|        |        |        |         |                                                                                                                       |      |         |       |
|--------|--------|--------|---------|-----------------------------------------------------------------------------------------------------------------------|------|---------|-------|
| M98045 | M98045 | 136510 | GEN-4C3 | synthetase mRNA, complete cds<br>Homo sapiens folypolyglutamate synthetase mRNA, complete cds                         | 1900 | 1830T>C | 3     |
| M98045 | M98045 | 136510 | GEN-4C3 | synthetase mRNA, complete cds<br>Homo sapiens folypolyglutamate synthetase mRNA, complete cds                         | 1900 | 1830T>C | 3     |
| M98045 | M98045 | 136510 | GEN-4C3 | synthetase mRNA, complete cds<br>Homo sapiens folypolyglutamate synthetase mRNA, complete cds                         | 1912 | 1842G>A | 3     |
| M98045 | M98045 | 136510 | GEN-4C3 | synthetase mRNA, complete cds<br>Homo sapiens folypolyglutamate synthetase mRNA, complete cds                         | 1995 | 1925C>G | 3     |
| MDCR   | L13385 | 601545 | GEN-106 | synthetase mRNA, complete cds<br>Homo sapiens(clone 71) Miller-Dieker lissencephaly protein (LIS1) mRNA, complete cds | 1467 | 1250C>T | 3     |
| MDCR   | L13385 | 601545 | GEN-106 | synthetase mRNA, complete cds<br>Homo sapiens(clone 71) Miller-Dieker lissencephaly protein (LIS1) mRNA, complete cds | 1868 | 1651C>T | 3     |
| MDCR   | L13385 | 601545 | GEN-106 | synthetase mRNA, complete cds<br>Homo sapiens(clone 71) Miller-Dieker lissencephaly protein (LIS1) mRNA, complete cds | 1917 | 1700C>T | 3     |
| MDCR   | L13385 | 601545 | GEN-106 | synthetase mRNA, complete cds<br>Homo sapiens(clone 71) Miller-Dieker lissencephaly protein (LIS1) mRNA, complete cds | 2962 | 2745G>T | 3     |
| MDCR   | L13385 | 601545 | GEN-106 | synthetase mRNA, complete cds<br>Homo sapiens(clone 71) Miller-Dieker lissencephaly protein (LIS1) mRNA, complete cds | 4589 | 4372G>A | 3     |
| MTP    | X75500 | 157147 | GEN-307 | synthetase mRNA, complete cds<br>H.sapiens mRNA for microsomal triglyceride transfer protein                          | 1847 | 1823T>G | F608C |

|        |        |        |         |                                                                    |      |         |       |
|--------|--------|--------|---------|--------------------------------------------------------------------|------|---------|-------|
| MTP    | X75500 | 157147 | GEN-307 | H.sapiens mRNA for microsomal triglyceride transfer protein        | 3231 | 3207G>A | 3     |
| NMOR1  | J03934 | 125860 | GEN-12L | Human, NAD(P)H:menadione oxidoreductase mRNA, complete cds         | 609  | 559C>T  | P187S |
| NMOR1  | J03934 | 125860 | GEN-12L | Human, NAD(P)H:menadione oxidoreductase mRNA, complete cds         | 1784 | 1734T>G | 3     |
| NMOR1  | J03934 | 125860 | GEN-12L | Human, NAD(P)H:menadione oxidoreductase mRNA, complete cds         | 1994 | 1944C>T | 3     |
| NMOR2  | J02888 | 160998 | GEN-XT  | Human, quinone oxidoreductase (NQO2) mRNA, complete cds            | 505  | 330G>A  | S     |
| NMOR2  | J02888 | 160998 | GEN-XT  | Human, quinone oxidoreductase (NQO2) mRNA, complete cds            | 909  | 734G>C  | 3     |
| NRAMP1 | L32185 | 600266 | GEN-21Y | Homo sapiens integral membrane protein (NRAMP1) mRNA, complete cds | 1399 | 1323C>T | S     |
| NRAMP2 | L37347 | 600523 | GEN-206 | Human integral membrane protein (Nramp2) mRNA, partial             | 1092 | 1083C>T | S     |
| ORM1   | M13692 | 138600 | GEN-1P5 | Human alpha-1 acid glycoprotein mRNA, complete cds                 | 128  | 113A>G  | Q38R  |
| ORM1   | M13692 | 138600 | GEN-1P5 | Human alpha-1 acid glycoprotein mRNA, complete cds                 | 222  | 207C>T  | S     |
| ORM1   | M13692 | 138600 | GEN-1P5 | Human alpha-1 acid glycoprotein mRNA, complete cds                 | 273  | 258A>C  | S     |
| ORM1   | M13692 | 138600 | GEN-1P5 | Human alpha-1 acid glycoprotein mRNA, complete cds                 | 296  | 281C>A  | T94N  |
| ORM1   | M13692 | 138600 | GEN-1P5 | Human alpha-1 acid glycoprotein mRNA, complete cds                 | 514  | 499C>T  | R167C |

|         |        |        |         |                                                          |      |              |       |
|---------|--------|--------|---------|----------------------------------------------------------|------|--------------|-------|
| ORM1    | M13692 | 138600 | 1P5     | glycoprotein mRNA, complete cds                          | 535  | 520G>A       | V174M |
| GEN-1P5 |        |        |         | Human alpha-1 acid glycoprotein mRNA, complete cds       | 654  | 639G>T       | 3     |
| ORM1    | M13692 | 138600 | GEN-1P5 | Human alpha-1 acid glycoprotein mRNA, complete cds       | 849  | 795A>G       | S     |
| PDHA1   | X52709 | 312170 | GEN-33Y | Human mRNA for brain pyruvate dehydrogenase (EC 1.2.4.1) | 1337 | 1283C>T      | 3     |
| PDHA1   | X52709 | 312170 | GEN-33Y | Human mRNA for brain pyruvate dehydrogenase (EC 1.2.4.1) | 1416 | 1362G>A      | 3     |
| PDHA1   | X52709 | 312170 | GEN-33Y | Human mRNA for brain pyruvate dehydrogenase (EC 1.2.4.1) | 116  | (-20)G>T     | 5     |
| PLA2G2A | M22430 | 172411 | GEN-25V | Human RASF-A PLA2 mRNA, complete cds                     | 231  | 96G>C        | S     |
| PLA2G2A | M22430 | 172411 | GEN-25V | Human RASF-A PLA2 mRNA, complete cds                     | 267  | 132C>T       | S     |
| PLA2G2A | M22430 | 172411 | GEN-25V | Human RASF-A PLA2 mRNA, complete cds                     | 267  | 132C>T       | S     |
| PLA2G2A | M22430 | 172411 | GEN-25V | Human RASF-A PLA2 mRNA, complete cds                     | 278  | 143-144GT>GT | S     |
| PLA2G2A | M22430 | 172411 | GEN-25V | Human RASF-A PLA2 mRNA, complete cds                     | 278  | 143-144delGT | F     |
| PLA2G2A | M22430 | 172411 | GEN-25V | Human RASF-A PLA2 mRNA, complete cds                     | 643  | 508C>T       | 3     |
| PLA2G2A | M22430 | 172411 | GEN-25V | Human RASF-A PLA2 mRNA, complete cds                     | 700  | 565G>C       | 3     |
| PLA2G2A | M22430 | 172411 | GEN-25V | Human RASF-A PLA2 mRNA, complete cds                     | 646  | 646G>T       | V216L |
| PNLIP   | M93285 | 246600 | GEN-48N | Pancreatic lipase (PNLIP) (Dietary supplement)           | 34   | 28G>T        | V10L  |
| PRSS1   | M22612 | 276000 | GEN-26A | Human pancreatic trypsin 1 (TRY1) mRNA, complete cds     | 61   | 55G>A        | D19N  |
| PRSS1   | M22612 | 276000 | GEN-26A | Human pancreatic trypsin 1 (TRY1) mRNA, complete cds     |      |              |       |

|         |        |        |         |                                                        |      |         |       |
|---------|--------|--------|---------|--------------------------------------------------------|------|---------|-------|
| PRSS1   | M22612 | 276000 | GEN-26A | Human pancreatic trypsin 1 (TRY1) mRNA, complete cds   | 97   | 91G>A   | E31K  |
| PRSS1   | M22612 | 276000 | GEN-26A | Human pancreatic trypsin 1 (TRY1) mRNA, complete cds   | 198  | 192C>T  | S     |
| PRSS1   | M22612 | 276000 | GEN-26A | Human pancreatic trypsin 1 (TRY1) mRNA, complete cds   | 412  | 406G>T  | G136C |
| PRSS1   | M22612 | 276000 | GEN-26A | Human pancreatic trypsin 1 (TRY1) mRNA, complete cds   | 492  | 486T>C  | S     |
| PRSS1   | M22612 | 276000 | GEN-26A | Human pancreatic trypsin 1 (TRY1) mRNA, complete cds   | 711  | 705C>T  | S     |
| PRSS1   | M22612 | 276000 | GEN-26A | Human pancreatic trypsin 1 (TRY1) mRNA, complete cds   | 744  | 738T>C  | S     |
| PRSS2   | M27602 | 601564 | GEN-2C7 | Human pancreatic trypsinogen (TRY2) mRNA, complete cds | 29   | 23C>T   | T8I   |
| PRSS2   | M27602 | 601564 | GEN-2C7 | Human pancreatic trypsinogen (TRY2) mRNA, complete cds | 34   | 28G>T   | V10F  |
| PRSS2   | M27602 | 601564 | GEN-2C7 | Human pancreatic trypsinogen (TRY2) mRNA, complete cds | 61   | 55G>A   | D19N  |
| PRSS2   | M27602 | 601564 | GEN-2C7 | Human pancreatic trypsinogen (TRY2) mRNA, complete cds | 97   | 91G>A   | E31K  |
| PRSS2   | M27602 | 601564 | GEN-2C7 | Human pancreatic trypsinogen (TRY2) mRNA, complete cds | 198  | 192C>T  | S     |
| PRSS2   | M27602 | 601564 | GEN-2C7 | Human pancreatic trypsinogen (TRY2) mRNA, complete cds | 276  | 270G>A  | S     |
| PXMP1   | X58528 | 170995 | GEN-392 | Human PMP70 mRNA for a peroxisomal membrane protein    | 2375 | 2351C>T | 3     |
| SLC18A3 | U09210 | 600336 | GEN-4F3 | Human vesicular acetylcholine transporter              | 1369 | 927A>G  | S     |

|         |        |        |         |                                                                               |      |           |   |
|---------|--------|--------|---------|-------------------------------------------------------------------------------|------|-----------|---|
| SLC18A3 | U09210 | 600336 | GEN-4F3 | mRNA, complete cds<br>Human vesicular<br>acetylcholine transporter            | 1567 | 1125C>G   | S |
| SLC18A3 | U09210 | 600336 | GEN-4F3 | mRNA, complete cds<br>Human vesicular<br>acetylcholine transporter            | 2080 | 1638G>T   | 3 |
| SLC18A3 | U09210 | 600336 | GEN-4F3 | mRNA, complete cds<br>Human vesicular<br>acetylcholine transporter            | 2199 | 1757G>A   | 3 |
| SLC18A3 | U09210 | 600336 | GEN-4F3 | mRNA, complete cds<br>Human vesicular<br>acetylcholine transporter            | 2349 | 1907G>T   | 3 |
| SLC5A1  | M24847 | 182380 | GEN-28S | mRNA, complete cds<br>Human Na <sup>+</sup> /glucose<br>cotransporter 1 mRNA, | 2226 | 2216C>T   | 3 |
| SLC6A3  | L24178 | 126455 | GEN-28S | complete cds<br>Homo sapiens dopamine<br>transporter mRNA,                    | 1917 | 1898C>T   | 3 |
| SOAT    | L21934 | 102642 | GEN-25C | complete cds<br>Human acyl coenzyme<br>A:cholesterol<br>acyltransferase mRNA, | 676  | (-721)T>G | 5 |
| SOAT    | L21934 | 102642 | GEN-25C | complete cds<br>Human acyl coenzyme<br>A:cholesterol<br>acyltransferase mRNA, | 814  | (-583)C>T | 5 |
| SOAT    | L21934 | 102642 | GEN-25C | complete cds<br>Human acyl coenzyme<br>A:cholesterol<br>acyltransferase mRNA, | 1993 | 597C>T    | S |
| SOAT    | L21934 | 102642 | GEN-25C | complete cds<br>Human acyl coenzyme<br>A:cholesterol<br>acyltransferase mRNA, | 2365 | 969C>T    | S |
| SOAT    | L21934 | 102642 | GEN-25C | complete cds<br>Human acyl coenzyme<br>A:cholesterol<br>acyltransferase mRNA, | 2821 | 1425G>C   | S |
| SOAT    | L21934 | 102642 | GEN-25C | complete cds<br>Human acyl coenzyme<br>A:cholesterol<br>acyltransferase mRNA, | 3537 | 2141T>C   | 3 |

|        |        |        |         |                                                                                            |      |         |       |
|--------|--------|--------|---------|--------------------------------------------------------------------------------------------|------|---------|-------|
| SOD2   | X07834 | 147460 | GEN-1ES | acyltransferase mRNA, complete cds                                                         | 44   | 40C>G   | P14A  |
| SOD2   | X07834 | 147460 | GEN-1ES | Human mRNA for manganese superoxide dismutase (EC 1.15.1.1)                                | 51   | 47T>C   | V16A  |
| SOD2   | X07834 | 147460 | GEN-1ES | Human mRNA for manganese superoxide dismutase (EC 1.15.1.1)                                | 198  | 194C>A  | T65N  |
| SOD2   | X07834 | 147460 | GEN-1ES | Human mRNA for manganese superoxide dismutase (EC 1.15.1.1)                                | 249  | 245T>C  | I82T  |
| SOD3   | J02947 | 185490 | GEN-Y3  | Human extracellular-superoxide dismutase (SOD3) mRNA, complete cds                         | 1042 | 973C>T  | 3     |
| SPINK1 | Y00705 | 167790 | GEN-UA  | Homo sapiens pstl mRNA for pancreatic secretory inhibitor (expressed in neoplastic tissue) | 332  | 272C>T  | 3     |
| TAP2   | Z22935 | 170261 | GEN-26P | H.sapiens TAP2B mRNA, complete CDS                                                         | 1163 | 1135G>A | V379I |
| TAP2   | Z22935 | 170261 | GEN-26P | H.sapiens TAP2B mRNA, complete CDS                                                         | 1186 | 1158G>T | S     |
| TAP2   | Z22935 | 170261 | GEN-26P | H.sapiens TAP2B mRNA, complete CDS                                                         | 1840 | 1812G>A | S     |
| TAP2   | Z22935 | 170261 | GEN-26P | H.sapiens TAP2B mRNA, complete CDS                                                         | 2021 | 1993G>A | A665T |
| TAP2   | Z22935 | 170261 | GEN-26P | H.sapiens TAP2B mRNA, complete CDS                                                         | 2087 | 2059C>T | F     |
| TAP2   | Z22935 | 170261 | GEN-26P | H.sapiens TAP2B mRNA, complete CDS                                                         | 2119 | 2091T>G | S     |
| TBG    | M14091 | 314200 | GEN-1QO | Human thyroxine-binding globulin mRNA, complete cds                                        | 901  | 571G>A  | D191N |
| TBG    | M14091 | 314200 | GEN-1QO | Human thyroxine-binding globulin mRNA, complete cds                                        | 1239 | 909G>T  | L303F |
| TCN2   | M60396 | 275350 | GEN-    | Human transcobalamin II                                                                    | 1164 | 1127C>T | S376L |

|        |        |        |         |                                                              |      |         |       |
|--------|--------|--------|---------|--------------------------------------------------------------|------|---------|-------|
| TCN2   | M60396 | 275350 | 3AX     | (TCII) mRNA, complete cds                                    | 1765 | 1728T>C | 3     |
| TPMT   | U12387 | 187680 | GEN-1LY | Human thiopurine methyltransferase (TPMT) mRNA, complete cds | 536  | 460G>A  | A154T |
| TPMT   | U12387 | 187680 | GEN-1LY | Human thiopurine methyltransferase (TPMT) mRNA, complete cds | 795  | 719A>G  | Y240C |
| TPMT   | U12387 | 187680 | GEN-1LY | Human thiopurine methyltransferase (TPMT) mRNA, complete cds | 1085 | 1009T>C | 3     |
| TPMT   | U12387 | 187680 | GEN-1LY | Human thiopurine methyltransferase (TPMT) mRNA, complete cds | 1336 | 1260C>T | 3     |
| TPMT   | U12387 | 187680 | GEN-1LY | Human thiopurine methyltransferase (TPMT) mRNA, complete cds | 1373 | 1297G>A | 3     |
| TPP2   | M55169 | 190470 | GEN-35U | Homo sapiens tripeptidyl peptidase II mRNA, 3 end            | 2681 | 2681T>G | F894C |
| TPP2   | M55169 | 190470 | GEN-35U | Homo sapiens tripeptidyl peptidase II mRNA, 3 end            | 3637 | 3637G>A | 3     |
| U03858 | U03858 | 600007 | GEN-MDM | Fms-related tyrosine kinase 3 ligand                         | 683  | 600C>T  | S     |
| U03858 | U03858 | 600007 | GEN-MDM | Fms-related tyrosine kinase 3 ligand                         | 1016 | 933T>C  | 3     |
| U06088 | U06088 | 253000 | GEN-MP3 | Human N-acetylgalactosamine 6-sulphatase (GALNS) gene        | 1936 | 1936C>T | 3     |
| U06088 | U06088 | 253000 | GEN-MP3 | Human N-acetylgalactosamine 6-sulphatase (GALNS) gene        | 2180 | 2180G>A | 3     |
| U06088 | U06088 | 253000 | GEN-MP3 | Human N-acetylgalactosamine 6-sulphatase (GALNS) gene        | 2221 | 2221G>A | 3     |
| U07132 | U07132 | 600380 | GEN-7M  | Orphan receptor                                              | 763  | 519G>A  | S     |
| U07132 | U07132 | 600380 | GEN-7M  | Orphan receptor                                              | 1399 | 1155C>T | S     |
| U07132 | U07132 | 600380 | GEN-7M  | Orphan receptor                                              | 1726 | 1482G>C | 3     |
| U07132 | U07132 | 600380 | GEN-7M  | Orphan receptor                                              | 1952 | 1708C>G | 3     |



|        |        |        |         |                                                                               |      |         |       |
|--------|--------|--------|---------|-------------------------------------------------------------------------------|------|---------|-------|
| U08021 | U08021 | 600008 | GEN-1FG | Human nicotinamide N-methyltransferase (NNMT) mRNA, complete cds              | 584  | 467C>G  | P156R |
| U08021 | U08021 | 600008 | GEN-1FG | Human nicotinamide N-methyltransferase (NNMT) mRNA, complete cds              | 613  | 496C>T  | S     |
| U08989 | U08989 | 133550 | GEN-CBZ | Human glutamate transporter mRNA, complete cds                                | 684  | 519C>T  | S     |
| U08989 | U08989 | 133550 | GEN-CBZ | Human glutamate transporter mRNA, complete cds                                | 1617 | 1452T>C | S     |
| U09178 | U09178 | 274270 | GEN-HA  | Dihydropyrimidine Dehydrogenase                                               | 166  | 85T>C   | C29R  |
| U09178 | U09178 | 274270 | GEN-HA  | Dihydropyrimidine Dehydrogenase                                               | 166  | 85T>C   | C29R  |
| U09178 | U09178 | 274270 | GEN-HA  | Dihydropyrimidine Dehydrogenase                                               | 577  | 496A>G  | M166V |
| U09178 | U09178 | 274270 | GEN-HA  | Dihydropyrimidine Dehydrogenase                                               | 638  | 557A>G  | Y186C |
| U09178 | U09178 | 274270 | GEN-HA  | Dihydropyrimidine Dehydrogenase                                               | 1708 | 1627A>G | I543V |
| U09178 | U09178 | 274270 | GEN-HA  | Dihydropyrimidine Dehydrogenase                                               | 3432 | 3351T>C | 3     |
| U09178 | U09178 | 274270 | GEN-HA  | Dihydropyrimidine Dehydrogenase                                               | 3730 | 3649G>A | 3     |
| U09178 | U09178 | 274270 | GEN-HA  | Dihydropyrimidine Dehydrogenase                                               | 3925 | 3844A>G | 3     |
| U09178 | U09178 | 274270 | GEN-HA  | Dihydropyrimidine Dehydrogenase                                               | 3937 | 3856T>C | 3     |
| U10868 | U10868 | 600466 | GEN-1JF | Human aldehyde dehydrogenase ALDH7 mRNA, complete cds                         | 2681 | 2634T>C | 3     |
| U16660 | U16660 | 600696 | GEN-1YD | Human peroxisomal enoyl-CoA hydratase-like protein (HPXEL) mRNA, complete cds | 149  | 122A>C  | E41A  |
| U16660 | U16660 | 600696 | GEN-1YD | Human peroxisomal enoyl-CoA hydratase-like protein (HPXEL) mRNA, complete cds | 402  | 375G>A  | S     |

|        |        |        |         |                                                                               |      |          |       |
|--------|--------|--------|---------|-------------------------------------------------------------------------------|------|----------|-------|
| U16660 | U16660 | 600696 | GEN-1YD | Human peroxisomal enoyl-CoA hydratase-like protein (HPXEL) mRNA, complete cds | 802  | 775C>G   | P259A |
| U16660 | U16660 | 600696 | GEN-1YD | Human peroxisomal enoyl-CoA hydratase-like protein (HPXEL) mRNA, complete cds | 1157 | 1130G>A  | 3     |
| U17986 | U17986 | 300036 | GEN-20X | Human GABA/noradrenaline transporter mRNA, complete cds                       | 1161 | 1132G>A  | V378M |
| U17986 | U17986 | 300036 | GEN-20X | Human GABA/noradrenaline transporter mRNA, complete cds                       | 1670 | 1641C>T  | S     |
| U17986 | U17986 | 300036 | GEN-20X | Human GABA/noradrenaline transporter mRNA, complete cds                       | 2034 | 2005G>A  | V669M |
| U17986 | U17986 | 300036 | GEN-20X | Human GABA/noradrenaline transporter mRNA, complete cds                       | 2088 | 2059C>T  | R687C |
| U17986 | U17986 | 300036 | GEN-20X | Human GABA/noradrenaline transporter mRNA, complete cds                       | 2150 | 2121C>T  | S     |
| U17986 | U17986 | 300036 | GEN-20X | Human GABA/noradrenaline transporter mRNA, complete cds                       | 2231 | 2202A>G  | 3     |
| U19720 | U19720 | 600424 | GEN-I1  | Folate Transporter (SLC19A1)                                                  | 53   | (-43)T>C | 5     |
| U19720 | U19720 | 600424 | GEN-I1  | Folate Transporter (SLC19A1)                                                  | 175  | 80G>A    | R27H  |
| U19720 | U19720 | 600424 | GEN-I1  | Folate Transporter (SLC19A1)                                                  | 175  | 80G>A    | R27H  |
| U19720 | U19720 | 600424 | GEN-I1  | Folate Transporter (SLC19A1)                                                  | 341  | 246C>G   | S     |
| U19720 | U19720 | 600424 | GEN-I1  | Folate Transporter (SLC19A1)                                                  | 791  | 696C>T   | S     |

|        |        |        |         |                                                                           |      |                   |       |
|--------|--------|--------|---------|---------------------------------------------------------------------------|------|-------------------|-------|
| U19720 | U19720 | 600424 | GEN-11  | (SLC19A1)<br>Folate Transporter                                           | 1067 | 972G>A            | S     |
| U19720 | U19720 | 600424 | GEN-11  | (SLC19A1)<br>Folate Transporter                                           | 2100 | 2005*2006ins<br>G | F     |
| U19720 | U19720 | 600424 | GEN-11  | (SLC19A1)<br>Folate Transporter                                           | 2582 | 2487T>G           | 3     |
| U19720 | U19720 | 600424 | GEN-11  | (SLC19A1)<br>Folate Transporter                                           | 2582 | 2487T>G           | 3     |
| U19720 | U19720 | 600424 | GEN-11  | (SLC19A1)<br>Folate Transporter                                           | 2617 | 2522C>T           | 3     |
| U19720 | U19720 | 600424 | GEN-11  | (SLC19A1)<br>Folate Transporter                                           | 2617 | 2522C>T           | 3     |
| U19720 | U19720 | 600424 | GEN-11  | (SLC19A1)<br>Folate Transporter                                           | 2652 | 2557T>C           | 3     |
| U19977 | U19977 | 600688 | GEN-22Q | Human<br>preprocarboxypeptidase<br>A2 (proCPA2) mRNA,<br>complete cds     | 631  | 627C>T            | S     |
| U20157 | U20157 | 601690 | GEN-234 | Human platelet-activating<br>factor acetylhydrolase<br>mRNA, complete cds | 1297 | 1136T>C           | V379A |
| U25029 | U25029 | 138040 | GEN-82  | Glucocorticoid receptor<br>alpha                                          | 335  | 335C>T            | 3     |
| U25029 | U25029 | 138040 | GEN-82  | Glucocorticoid receptor<br>alpha                                          | 386  | 386T>C            | 3     |
| U25029 | U25029 | 138040 | GEN-82  | Glucocorticoid receptor<br>alpha                                          | 1069 | 1069C>T           | 3     |
| U27699 | U27699 | 603080 | GEN-2C9 | Human pephBGT-1<br>betaine-GABA transporter<br>mRNA, complete cds         | 2841 | 2255C>T           | 3     |
| U34252 | U34252 | 602733 | GEN-3O5 | Human gamma-<br>aminobutyraldehyde<br>dehydrogenase mRNA,<br>complete cds | 2417 | 2040G>A           | 3     |
| U34252 | U34252 | 602733 | GEN-3O5 | Human gamma-<br>aminobutyraldehyde<br>dehydrogenase mRNA,<br>complete cds | 2471 | 2094A>C           | 3     |
| U34252 | U34252 | 602733 | GEN-3O5 | Human gamma-<br>aminobutyraldehyde<br>dehydrogenase mRNA,<br>complete cds | 2674 | 2297A>C           | 3     |

|        |        |        |         |                                                                                                     |      |         |       |
|--------|--------|--------|---------|-----------------------------------------------------------------------------------------------------|------|---------|-------|
| U34252 | U34252 | 602733 | GEN-305 | dehydrogenase mRNA, complete cds<br>Human gamma-aminobutyraldehyde dehydrogenase mRNA, complete cds | 2676 | 2299A>C | 3     |
| U35735 | U35735 | 111000 | GEN-2MN | Human RACH1 (RACH1) mRNA, complete cds                                                              | 1006 | 838A>G  | N280D |
| U35735 | U35735 | 111000 | GEN-2MN | Human RACH1 (RACH1) mRNA, complete cds                                                              | 2619 | 2451T>C | 3     |
| U35735 | U35735 | 111000 | GEN-2MN | Human RACH1 (RACH1) mRNA, complete cds                                                              | 2706 | 2538T>C | 3     |
| U36601 | U36601 | 603268 | GEN-IR  | Human RACH1 (RACH1) mRNA, complete cds                                                              | 2727 | 2700T>G | 3     |
| U36601 | U36601 | 603268 | GEN-IR  | Heparan N-deacetylase/N-sulfotransferase-2                                                          | 2972 | 2945A>G | 3     |
| U37143 | U37143 | 601258 | GEN-2NS | Heparan N-deacetylase/N-sulfotransferase-2                                                          | 338  | 333G>C  | S     |
| U37143 | U37143 | 601258 | GEN-2NS | Human cytochrome P450 monooxygenase CYP2J2 mRNA, complete cds                                       | 1545 | 1540C>T | 3     |
| U53347 | U53347 | 109190 | GEN-34A | Human cytochrome P450 monooxygenase CYP2J2 mRNA, complete cds                                       | 2868 | 2249A>T | 3     |
| U55206 | U55206 | None   | GEN-35Z | Human neutral amino acid transporter B mRNA, complete cds                                           | 75   | 16T>C   | C6R   |
| U55206 | U55206 | None   | GEN-35Z | Homo sapiens human gamma-glutamyl hydrolase (hGH) mRNA, complete cds                                | 150  | 91G>A   | A31T  |
| U55206 | U55206 | None   | GEN-35Z | Homo sapiens human gamma-glutamyl hydrolase (hGH) mRNA, complete cds                                | 511  | 452C>T  | T151I |
| U55206 | U55206 | None   | GEN-35Z | Homo sapiens human gamma-glutamyl hydrolase (hGH) mRNA, complete cds                                | 1161 | 1102A>G | 3     |

|        |        |        |             |                                                                                            |      |         |   |
|--------|--------|--------|-------------|--------------------------------------------------------------------------------------------|------|---------|---|
| U70867 | U70867 | 601460 | GEN-4S      | prostaglandin transporter<br>hPGT                                                          | 2706 | 2615T>G | 3 |
| U70867 | U70867 | 601460 | GEN-4S      | prostaglandin transporter<br>hPGT                                                          | 2839 | 2748T>A | 3 |
| U70867 | U70867 | 601460 | GEN-4S      | prostaglandin transporter<br>hPGT                                                          | 2908 | 2817A>G | 3 |
| U70867 | U70867 | 601460 | GEN-4S      | prostaglandin transporter<br>hPGT                                                          | 3171 | 3080A>G | 3 |
| U70867 | U70867 | 601460 | GEN-4S      | prostaglandin transporter<br>hPGT                                                          | 3171 | 3080A>G | 3 |
| U70867 | U70867 | 601460 | GEN-4S      | prostaglandin transporter<br>hPGT                                                          | 3253 | 3162A>G | 3 |
| U70867 | U70867 | 601460 | GEN-4S      | prostaglandin transporter<br>hPGT                                                          | 3255 | 3164A>G | 3 |
| U70867 | U70867 | 601460 | GEN-4S      | prostaglandin transporter<br>hPGT                                                          | 3594 | 3503T>A | 3 |
| U79745 | U79745 | None   | GEN-<br>LPT | Homo sapiens<br>monocarboxylate<br>transporter homologue<br>MCT6 mRNA, complete<br>cds     | 2095 | 1930G>A | 3 |
| U81375 | U81375 | 602193 | GEN-<br>3VO | Human placental<br>equilibrative nucleoside<br>transporter 1 (hENT1)<br>mRNA, complete cds | 1989 | 1811G>A | 3 |
| U81375 | U81375 | 602193 | GEN-<br>3VO | Human placental<br>equilibrative nucleoside<br>transporter 1 (hENT1)<br>mRNA, complete cds | 1996 | 1818C>T | 3 |
| U81375 | U81375 | 602193 | GEN-<br>3VO | Human placental<br>equilibrative nucleoside<br>transporter 1 (hENT1)<br>mRNA, complete cds | 2045 | 1867T>C | 3 |
| U81800 | U81800 | None   | GEN-<br>3WB | Homo sapiens<br>monocarboxylate<br>transporter (MCT3) mRNA,<br>complete cds                | 1624 | 1562G>C | 3 |
| U92314 | U92314 | 604125 | GEN-<br>47U | Homo sapiens<br>hydroxysteroid<br>sulfotransferase<br>SULT2B1a (HSST2)                     | 1146 | 771C>T  | S |

|        |        |        |         |                                                                                              |      |         |       |
|--------|--------|--------|---------|----------------------------------------------------------------------------------------------|------|---------|-------|
| U92314 | U92314 | 604125 | GEN-47U | mRNA, complete cds<br>Homo sapiens<br>hydroxysteroid<br>sulfotransferase<br>SULT2B1a (HSST2) | 1164 | 789C>T  | S     |
| U92314 | U92314 | 604125 | GEN-47U | mRNA, complete cds<br>Homo sapiens<br>hydroxysteroid<br>sulfotransferase<br>SULT2B1a (HSST2) | 1278 | 903T>C  | S     |
| V00494 | V00494 | 103600 | GEN-TL  | mRNA, complete cds<br>Human messenger RNA<br>for serum albumin (HSA)                         | 34   | (-6)G>T | 5     |
| V00494 | V00494 | 103600 | GEN-TL  | Human messenger RNA<br>for serum albumin (HSA)                                               | 36   | (-4)C>G | 5     |
| V00494 | V00494 | 103600 | GEN-TL  | Human messenger RNA<br>for serum albumin (HSA)                                               | 401  | 362G>A  | G121E |
| V00494 | V00494 | 103600 | GEN-TL  | Human messenger RNA<br>for serum albumin (HSA)                                               | 431  | 392A>G  | D131G |
| V00494 | V00494 | 103600 | GEN-TL  | Human messenger RNA<br>for serum albumin (HSA)                                               | 1090 | 1051T>C | S     |
| V00494 | V00494 | 103600 | GEN-TL  | Human messenger RNA<br>for serum albumin (HSA)                                               | 1091 | 1052T>G | L351W |
| V00494 | V00494 | 103600 | GEN-TL  | Human messenger RNA<br>for serum albumin (HSA)                                               | 1531 | 1492A>C | T498P |
| V00494 | V00494 | 103600 | GEN-TL  | Human messenger RNA<br>for serum albumin (HSA)                                               | 1533 | 1494C>A | S     |
| V00494 | V00494 | 103600 | GEN-TL  | Human messenger RNA<br>for serum albumin (HSA)                                               | 1637 | 1598T>C | F533S |
| V00494 | V00494 | 103600 | GEN-TL  | Human messenger RNA<br>for serum albumin (HSA)                                               | 1707 | 1668C>T | S     |
| V00494 | V00494 | 103600 | GEN-TL  | Human messenger RNA<br>for serum albumin (HSA)                                               | 1719 | 1680G>A | S     |
| V00494 | V00494 | 103600 | GEN-TL  | Human messenger RNA<br>for serum albumin (HSA)                                               | 1926 | 1887T>A | 3     |
| V00594 | V00594 | 156360 | GEN-P6  | Human mRNA for<br>metallothionein from<br>cadmium-treated cells                              | 320  | 263G>C  | 3     |
| X02317 | X02317 | 147450 | GEN-KM  | Superoxide dismutase 1<br>(Cu/Zn)                                                            | 614  | 550A>C  | 3     |
| X02920 | X02920 | 107400 | GEN-PH  | Human mRNA for alpha 1-                                                                      | 107  | 107T>C  | L36P  |

|        |        |        |         |                                                                        |      |             |       |
|--------|--------|--------|---------|------------------------------------------------------------------------|------|-------------|-------|
| X02920 | X02920 | 107400 | GEN-PH  | antitrypsin carboxyterminal region (aa 268-394)                        | 137  | 137G>A      | S46N  |
| X02920 | X02920 | 107400 | GEN-PH  | Human mRNA for alpha 1-antitrypsin carboxyterminal region (aa 268-394) | 195  | 195C>T      | S     |
| X02920 | X02920 | 107400 | GEN-PH  | Human mRNA for alpha 1-antitrypsin carboxyterminal region (aa 268-394) | 327  | 327A>C      | E109D |
| X03438 | X03438 | 138970 | GEN-PM  | Human mRNA for granulocyte colony-stimulating factor (G-CSF)           | 586  | 555G>A      | S     |
| X03438 | X03438 | 138970 | GEN-PM  | Human mRNA for granulocyte colony-stimulating factor (G-CSF)           | 1235 | 1204C>T     | 3     |
| X03663 | X03663 | 164770 | GEN-51  | Colony stimulating factor 1 receptor                                   | 3732 | 3432T>C     | 3     |
| X03663 | X03663 | 164770 | GEN-51  | Colony stimulating factor 1 receptor                                   | 3951 | 3651C>A     | 3     |
| X08006 | X08006 | None   | GEN-1FE | Human mRNA for cytochrome P450 db1                                     | 100  | 100C>T      | P34S  |
| X08006 | X08006 | None   | GEN-1FE | Human mRNA for cytochrome P450 db1                                     | 124  | 124G>A      | G42R  |
| X08006 | X08006 | None   | GEN-1FE | Human mRNA for cytochrome P450 db1                                     | 137  | 137^138insT | F     |
| X08006 | X08006 | None   | GEN-1FE | Human mRNA for cytochrome P450 db1                                     | 271  | 271C>G      | L91V  |
| X08006 | X08006 | None   | GEN-1FE | Human mRNA for cytochrome P450 db1                                     | 281  | 281A>G      | H94R  |
| X08006 | X08006 | None   | GEN-1FE | Human mRNA for cytochrome P450 db1                                     | 294  | 294C>G      | S     |
| X08006 | X08006 | None   | GEN-1FE | Human mRNA for cytochrome P450 db1                                     | 336  | 336C>T      | S     |
| X08006 | X08006 | None   | GEN-1FE | Human mRNA for cytochrome P450 db1                                     | 408  | 408G>C      | S     |
| X08006 | X08006 | None   | GEN-1FE | Human mRNA for cytochrome P450 db1                                     | 408  | 408G>C      | S     |
| X08006 | X08006 | None   | GEN-1FE | Human mRNA for cytochrome P450 db1                                     | 454  | 454delT     | F     |

|        |        |      |         |                                    |      |               |         |
|--------|--------|------|---------|------------------------------------|------|---------------|---------|
| X08006 | X08006 | None | GEN-1FE | Human mRNA for cytochrome P450 db1 | 505  | 505G>T        | F       |
| X08006 | X08006 | None | GEN-1FE | Human mRNA for cytochrome P450 db1 | 635  | 635G>A        | G212E   |
| X08006 | X08006 | None | GEN-1FE | Human mRNA for cytochrome P450 db1 | 692  | 692T>C        | L231P   |
| X08006 | X08006 | None | GEN-1FE | Human mRNA for cytochrome P450 db1 | 696  | 696T>C        | S       |
| X08006 | X08006 | None | GEN-1FE | Human mRNA for cytochrome P450 db1 | 775  | 775delA       | F       |
| X08006 | X08006 | None | GEN-1FE | Human mRNA for cytochrome P450 db1 | 801  | 801C>A        | S       |
| X08006 | X08006 | None | GEN-1FE | Human mRNA for cytochrome P450 db1 | 836  | 836T>A        | M279K   |
| X08006 | X08006 | None | GEN-1FE | Human mRNA for cytochrome P450 db1 | 839  | 839-841AGA>AG | S       |
| X08006 | X08006 | None | GEN-1FE | Human mRNA for cytochrome P450 db1 | 839  | 839-841delAGA | K281del |
| X08006 | X08006 | None | GEN-1FE | Human mRNA for cytochrome P450 db1 | 840  | 840-842GAA>GA | S       |
| X08006 | X08006 | None | GEN-1FE | Human mRNA for cytochrome P450 db1 | 840  | 840-842delGAA | K281del |
| X08006 | X08006 | None | GEN-1FE | Human mRNA for cytochrome P450 db1 | 854  | 854A>G        | N285S   |
| X08006 | X08006 | None | GEN-1FE | Human mRNA for cytochrome P450 db1 | 886  | 886C>T        | R296C   |
| X08006 | X08006 | None | GEN-1FE | Human mRNA for cytochrome P450 db1 | 971  | 971A>C        | H324P   |
| X08006 | X08006 | None | GEN-1FE | Human mRNA for cytochrome P450 db1 | 1108 | 1108G>A       | V370I   |
| X08006 | X08006 | None | GEN-1FE | Human mRNA for cytochrome P450 db1 | 1203 | 1203G>A       | S       |
| X08006 | X08006 | None | GEN-1FE | Human mRNA for cytochrome P450 db1 | 1262 | 1262T>C       | L421P   |
| X08006 | X08006 | None | GEN-1FE | Human mRNA for cytochrome P450 db1 | 1401 | 1401G>C       | S       |
| X08006 | X08006 | None | GEN-1FE | Human mRNA for cytochrome P450 db1 | 1457 | 1457G>C       | S486T   |
| X08006 | X08006 | None | GEN-1FE | Human mRNA for cytochrome P450 db1 | 1457 | 1457G>C       | S486T   |



|        |        |        |                    |                                                                           |      |          |       |
|--------|--------|--------|--------------------|---------------------------------------------------------------------------|------|----------|-------|
| X12387 | X12387 | 124010 | 1FE<br>GEN-<br>1LZ | cytochrome P450 db1<br>Human mRNA for<br>cytochrome P-450 (cyp3<br>locus) | 44   | (-26)G>C | 5     |
| X12387 | X12387 | 124010 | GEN-<br>1LZ        | Human mRNA for<br>cytochrome P-450 (cyp3<br>locus)                        | 628  | 559A>T   | T187S |
| X12387 | X12387 | 124010 | GEN-<br>1LZ        | Human mRNA for<br>cytochrome P-450 (cyp3<br>locus)                        | 646  | 577A>G   | I193V |
| X12387 | X12387 | 124010 | GEN-<br>1LZ        | Human mRNA for<br>cytochrome P-450 (cyp3<br>locus)                        | 676  | 607T>C   | F203L |
| X12387 | X12387 | 124010 | GEN-<br>1LZ        | Human mRNA for<br>cytochrome P-450 (cyp3<br>locus)                        | 823  | 754T>G   | S252A |
| X12387 | X12387 | 124010 | GEN-<br>1LZ        | Human mRNA for<br>cytochrome P-450 (cyp3<br>locus)                        | 1361 | 1292T>C  | I431T |
| X12387 | X12387 | 124010 | GEN-<br>1LZ        | Human mRNA for<br>cytochrome P-450 (cyp3<br>locus)                        | 2189 | 2120G>A  | 3     |
| X13561 | X13561 | 147910 | GEN-<br>1OH        | Human mRNA for<br>preprokallikrein (EC 3.4.21)                            | 54   | 18G>T    | S     |
| X13561 | X13561 | 147910 | GEN-<br>1OH        | Human mRNA for<br>preprokallikrein (EC 3.4.21)                            | 441  | 405T>C   | S     |
| X13561 | X13561 | 147910 | GEN-<br>1OH        | Human mRNA for<br>preprokallikrein (EC 3.4.21)                            | 469  | 433G>C   | E145Q |
| X13561 | X13561 | 147910 | GEN-<br>1OH        | Human mRNA for<br>preprokallikrein (EC 3.4.21)                            | 592  | 556A>G   | K186E |
| X13589 | X13589 | 107910 | GEN-56             | Cytochrome P450,<br>subfamily XIX<br>(aromatization of<br>androgens)      | 364  | 240A>G   | S     |
| X13589 | X13589 | 107910 | GEN-56             | Cytochrome P450,<br>subfamily XIX<br>(aromatization of<br>androgens)      | 914  | 790C>T   | R264C |
| X13589 | X13589 | 107910 | GEN-56             | Cytochrome P450,<br>subfamily XIX<br>(aromatization of<br>androgens)      | 914  | 790C>T   | R264C |

|        |        |        |         |                                                                                    |      |         |       |
|--------|--------|--------|---------|------------------------------------------------------------------------------------|------|---------|-------|
| X13589 | X13589 | 107910 | GEN-56  | androgens)<br>Cytochrome P450,<br>subfamily XIX<br>(aromatization of<br>androgens) | 1655 | 1531C>T | 3     |
| X13589 | X13589 | 107910 | GEN-56  | Cytochrome P450,<br>subfamily XIX<br>(aromatization of<br>androgens)               | 1796 | 1672G>T | 3     |
| X13930 | X13930 | 122720 | GEN-1Q3 | Human CYP2A4 mRNA for<br>P-450 IIA4 protein                                        | 60   | 51A>G   | S     |
| X13930 | X13930 | 122720 | GEN-1Q3 | Human CYP2A4 mRNA for<br>P-450 IIA4 protein                                        | 255  | 246T>C  | S     |
| X13930 | X13930 | 122720 | GEN-1Q3 | Human CYP2A4 mRNA for<br>P-450 IIA4 protein                                        | 272  | 263G>A  | R88K  |
| X13930 | X13930 | 122720 | GEN-1Q3 | Human CYP2A4 mRNA for<br>P-450 IIA4 protein                                        | 1072 | 1063G>A | V355M |
| X13930 | X13930 | 122720 | GEN-1Q3 | Human CYP2A4 mRNA for<br>P-450 IIA4 protein                                        | 1146 | 1137G>A | S     |
| X13930 | X13930 | 122720 | GEN-1Q3 | Human CYP2A4 mRNA for<br>P-450 IIA4 protein                                        | 1485 | 1476G>T | S     |
| X13930 | X13930 | 122720 | GEN-1Q3 | Human CYP2A4 mRNA for<br>P-450 IIA4 protein                                        | 1675 | 1666A>T | 3     |
| X13930 | X13930 | 122720 | GEN-1Q3 | Human CYP2A4 mRNA for<br>P-450 IIA4 protein                                        | 1677 | 1668C>G | 3     |
| X13930 | X13930 | 122720 | GEN-1Q3 | Human CYP2A4 mRNA for<br>P-450 IIA4 protein                                        | 1697 | 1688C>A | 3     |
| X16699 | X16699 | 124075 | GEN-1YJ | Human mRNA for<br>cytochrome P-450HP                                               | 1064 | 1064T>G | F355C |
| X52773 | X52773 | 180245 | GEN-74  | Retinoid X receptor, alpha                                                         | 1744 | 1669G>A | 3     |
| X56199 | X56199 | None   | GEN-36T | Human XIST, coding<br>sequence a mRNA (locus<br>DXS399E)                           | 1338 | 1339T>G | 3     |
| X57522 | X57522 | 170260 | GEN-37W | H.sapiens RING4 cDNA                                                               | 1207 | 1177A>G | I393V |
| X57522 | X57522 | 170260 | GEN-37W | H.sapiens RING4 cDNA                                                               | 2120 | 2090A>G | D697G |
| X59498 | X59498 | 176300 | GEN-RU  | H.sapiens ttr mRNA for<br>transthyretin                                            | 92   | 71G>A   | G24D  |
| X59498 | X59498 | 176300 | GEN-RU  | H.sapiens ttr mRNA for<br>transthyretin                                            | 177  | 156G>T  | S     |

|        |        |        |         |                                                     |      |           |       |
|--------|--------|--------|---------|-----------------------------------------------------|------|-----------|-------|
| X59498 | X59498 | 176300 | GEN-RU  | H.sapiens ttr mRNA for transthyretin                | 380  | 359C>T    | S120F |
| X60069 | X60069 | 231950 | GEN-3AJ | Human mRNA for pancreatic gamma-glutamyltransferase | 102  | (-257)G>A | 5     |
| X60069 | X60069 | 231950 | GEN-3AJ | Human mRNA for pancreatic gamma-glutamyltransferase | 336  | (-23)C>T  | 5     |
| X60069 | X60069 | 231950 | GEN-3AJ | Human mRNA for pancreatic gamma-glutamyltransferase | 1173 | 815C>T    | A272V |
| X60069 | X60069 | 231950 | GEN-3AJ | Human mRNA for pancreatic gamma-glutamyltransferase | 1173 | 815C>T    | A272V |
| X60069 | X60069 | 231950 | GEN-3AJ | Human mRNA for pancreatic gamma-glutamyltransferase | 1399 | 1041C>T   | S     |
| X60069 | X60069 | 231950 | GEN-3AJ | Human mRNA for pancreatic gamma-glutamyltransferase | 1409 | 1051G>T   | A351S |
| X60069 | X60069 | 231950 | GEN-3AJ | Human mRNA for pancreatic gamma-glutamyltransferase | 1482 | 1124C>T   | T375M |
| X60069 | X60069 | 231950 | GEN-3AJ | Human mRNA for pancreatic gamma-glutamyltransferase | 1591 | 1233G>A   | S     |
| X60069 | X60069 | 231950 | GEN-3AJ | Human mRNA for pancreatic gamma-glutamyltransferase | 1624 | 1266C>T   | S     |
| X60069 | X60069 | 231950 | GEN-3AJ | Human mRNA for pancreatic gamma-glutamyltransferase | 1637 | 1279C>A   | P427T |
| X60069 | X60069 | 231950 | GEN-3AJ | Human mRNA for pancreatic gamma-glutamyltransferase | 1651 | 1293C>T   | S     |
| X60069 | X60069 | 231950 | GEN-3AJ | Human mRNA for pancreatic gamma-glutamyltransferase | 1662 | 1304T>C   | V435A |
| X60069 | X60069 | 231950 | GEN-3AJ | Human mRNA for pancreatic gamma-glutamyltransferase | 1783 | 1425A>G   | S     |

|        |        |        |         |                                                        |      |         |       |
|--------|--------|--------|---------|--------------------------------------------------------|------|---------|-------|
| X60069 | X60069 | 231950 | GEN-3AJ | Human mRNA for pancreatic gamma-glutamyltransferase    | 1794 | 1436C>T | T479M |
| X60069 | X60069 | 231950 | GEN-3AJ | Human mRNA for pancreatic gamma-glutamyltransferase    | 1795 | 1437G>A | S     |
| X60069 | X60069 | 231950 | GEN-3AJ | Human mRNA for pancreatic gamma-glutamyltransferase    | 1981 | 1623C>T | S     |
| X60069 | X60069 | 231950 | GEN-3AJ | Human mRNA for pancreatic gamma-glutamyltransferase    | 2007 | 1649C>T | T550M |
| X60069 | X60069 | 231950 | GEN-3AJ | Human mRNA for pancreatic gamma-glutamyltransferase    | 2031 | 1673C>T | S558L |
| X60069 | X60069 | 231950 | GEN-3AJ | Human mRNA for pancreatic gamma-glutamyltransferase    | 2047 | 1689C>T | S     |
| X60069 | X60069 | 231950 | GEN-3AJ | Human mRNA for pancreatic gamma-glutamyltransferase    | 2147 | 1789C>T | 3     |
| X60069 | X60069 | 231950 | GEN-3AJ | Human mRNA for pancreatic gamma-glutamyltransferase    | 2176 | 1818C>T | 3     |
| X60069 | X60069 | 231950 | GEN-3AJ | Human mRNA for pancreatic gamma-glutamyltransferase    | 2224 | 1866C>A | 3     |
| X63359 | X63359 | 600070 | GEN-3DC | H.sapiens UGT2B10 mRNA for udp glucuronosyltransferase | 1516 | 1506C>T | S     |
| X63359 | X63359 | 600070 | GEN-3DC | H.sapiens UGT2B10 mRNA for udp glucuronosyltransferase | 2714 | 2704G>A | 3     |
| X63522 | X63522 | 180246 | GEN-75  | MHC class I promoter binding protein                   | 1331 | 1152T>C | S     |
| X64177 | X64177 | 156351 | GEN-3EQ | H.sapiens mRNA for metallothionein                     | 63   | 40G>A   | A14T  |
| X64177 | X64177 | 156351 | GEN-3EQ | H.sapiens mRNA for metallothionein                     | 90   | 67A>G   | K23E  |
| X64177 | X64177 | 156351 | GEN-3EQ | H.sapiens mRNA for metallothionein                     | 125  | 102C>T  | S     |

|        |        |        |         |                                                             |      |         |       |
|--------|--------|--------|---------|-------------------------------------------------------------|------|---------|-------|
| X64177 | X64177 | 156351 | GEN-3EQ | H.sapiens mRNA for metallothionein                          | 131  | 108T>C  | S     |
| X64177 | X64177 | 156351 | GEN-3EQ | H.sapiens mRNA for metallothionein                          | 168  | 145A>G  | I49V  |
| X64177 | X64177 | 156351 | GEN-3EQ | H.sapiens mRNA for metallothionein                          | 182  | 159G>A  | S     |
| X68836 | X68836 | 601468 | GEN-3IR | H.sapiens mRNA for S-adenosylmethionine synthetase          | 240  | 175G>A  | V59I  |
| X71440 | X71440 | None   | GEN-3KS | H.sapiens mRNA for peroxisomal acyl-CoA oxidase             | 949  | 936G>C  | M312I |
| X78282 | X78282 | 601292 | GEN-LVF | H.sapiens mRNA for aryl sulfotransferase (ST1A2)            | 895  | 895T>C  | 3     |
| X79389 | X79389 | 600436 | GEN-3T7 | H.sapiens GSTT1 mRNA                                        | 824  | 824T>C  | 3     |
| X86681 | X86681 | 602110 | GEN-41E | H.sapiens mRNA for nucleolar protein, HNP36                 | 1725 | 1340G>A | 3     |
| X90908 | X90908 | 600422 | GEN-LSA | H.sapiens mRNA for I-15P (I-BABP) protein                   | 364  | 236C>T  | T79M  |
| X90999 | X90999 | 138760 | GEN-477 | H.sapiens mRNA for Glyoxalase II                            | 950  | 914A>G  | 3     |
| X95190 | X95190 | 601641 | GEN-49Y | H.sapiens mRNA for Branched chain Acyl-CoA Oxidase          | 1394 | 1302C>T | S     |
| X95190 | X95190 | 601641 | GEN-49Y | H.sapiens mRNA for Branched chain Acyl-CoA Oxidase          | 1934 | 1842C>A | S     |
| X96395 | X96395 | 601107 | GEN-4AM | H.sapiens mRNA for canalicular multidrug resistance protein | 848  | 811G>T  | A271S |
| X97868 | X97868 | 300003 | GEN-LTH | H.sapiens mRNA for arylsulphatase                           | 1652 | 1582T>C | Y528H |
| X98332 | X98332 | 602607 | GEN-MMA | H.sapiens mRNA for organic cation transporter, liver        | 630  | 558C>T  | S     |
| XDH    | U06117 | 278300 | GEN-194 | Human xanthine dehydrogenase (XDH) mRNA, complete cds       | 3951 | 3888C>G | S     |
| Y00498 | Y00498 | 601129 | GEN-9N  | Cytochrome P450, subfamily I1C (mephenytoin                 | 431  | 389C>A  | T130N |

|        |        |        |        |                                                                                    |      |         |       |
|--------|--------|--------|--------|------------------------------------------------------------------------------------|------|---------|-------|
| Y00498 | Y00498 | 601129 | GEN-9N | 4-hydroxylase)<br>Cytochrome P450,<br>subfamily IIC (mephenytoin<br>4-hydroxylase) | 489  | 447T>C  | S     |
| Y00498 | Y00498 | 601129 | GEN-9N | Cytochrome P450,<br>subfamily IIC (mephenytoin<br>4-hydroxylase)                   | 491  | 449A>G  | H150R |
| Y00498 | Y00498 | 601129 | GEN-9N | Cytochrome P450,<br>subfamily IIC (mephenytoin<br>4-hydroxylase)                   | 522  | 480G>T  | K160N |
| Y00498 | Y00498 | 601129 | GEN-9N | Cytochrome P450,<br>subfamily IIC (mephenytoin<br>4-hydroxylase)                   | 525  | 483T>C  | S     |
| Y00498 | Y00498 | 601129 | GEN-9N | Cytochrome P450,<br>subfamily IIC (mephenytoin<br>4-hydroxylase)                   | 582  | 540C>T  | S     |
| Y00498 | Y00498 | 601129 | GEN-9N | Cytochrome P450,<br>subfamily IIC (mephenytoin<br>4-hydroxylase)                   | 583  | 541G>A  | V181I |
| Y00498 | Y00498 | 601129 | GEN-9N | Cytochrome P450,<br>subfamily IIC (mephenytoin<br>4-hydroxylase)                   | 834  | 792C>G  | I264M |
| Y00498 | Y00498 | 601129 | GEN-9N | Cytochrome P450,<br>subfamily IIC (mephenytoin<br>4-hydroxylase)                   | 999  | 957C>G  | S     |
| Y00498 | Y00498 | 601129 | GEN-9N | Cytochrome P450,<br>subfamily IIC (mephenytoin<br>4-hydroxylase)                   | 1539 | 1497T>C | 3     |

Table 15.  
Identified  
Variances  
In Genes  
for  
Pathways  
Identified  
in  
Inflammati  
on and  
Immune  
Disease

|          |          |        |         |                                                             |      |         |       |
|----------|----------|--------|---------|-------------------------------------------------------------|------|---------|-------|
| AB00022  | AB00022  | None   | GEN-16K | Homo sapiens mRNA for CC chemokine, complete cds            | 427  | 364C>T  | 3     |
| AB00050  | AB00050  | 602356 | GEN-161 | Homo sapiens mRNA for TRAF5, complete cds                   | 2185 | 2131A>T | 3     |
| AB00088  | AB00088  | 602227 | GEN-14F | Human mRNA for EBI1-ligand chemokine, complete cds          | 627  | 489G>A  | 3     |
| AB00240  | AB00240  | 602737 | GEN-1A1 | Homo sapiens mRNA for SLC, complete cds                     | 794  | 736T>G  | 3     |
| AB02068  | AB02068  | None   | GEN-LAX | Homo sapiens mRNA for KIAA0873 protein, partial cds         | 3854 | 3854A>G | 3     |
| AC00577  | AC00577  | None   | GEN-ML4 | Homo sapiens chromosome 19, cosmid F20237                   | 1492 | 1482G>A | 3     |
| AF000234 | AF000234 | 600846 | GEN-16J | PURINERGIC RECEPTOR P2X, LIGAND-GATED ION CHANNEL, 4; P2RX4 | 365  | 365C>T  | P122L |
| AF000234 | AF000234 | 600846 | GEN-16J | PURINERGIC RECEPTOR P2X, LIGAND-GATED ION CHANNEL, 4; P2RX4 | 381  | 381G>A  | S     |
| AF000234 | AF000234 | 600846 | GEN-16J | PURINERGIC RECEPTOR P2X, LIGAND-GATED ION CHANNEL, 4; P2RX4 | 624  | 624A>G  | S     |
| AF000234 | AF000234 | 600846 | GEN-16J | PURINERGIC RECEPTOR P2X, LIGAND-GATED ION CHANNEL, 4; P2RX4 | 641  | 641C>T  | P214L |
| AF000234 | AF000234 | 600846 | GEN-16J | PURINERGIC RECEPTOR P2X, LIGAND-GATED ION CHANNEL, 4; P2RX4 | 1161 | 1161T>C | 3     |
| AF000571 | AF000571 | 192500 | GEN-15U | K+ channel (KvLQT1)                                         | 545  | 435C>T  | S     |
| AF000571 | AF000571 | 192500 | GEN-15U | K+ channel (KvLQT1)                                         | 1748 | 1638G>A | S     |
| AF000571 | AF000571 | 192500 | GEN-15U | K+ channel (KvLQT1)                                         | 2360 | 2250G>A | 3     |
| AF000571 | AF000571 | 192500 | GEN-15U | K+ channel (KvLQT1)                                         | 2552 | 2442C>T | 3     |
| AF000571 | AF000571 | 192500 | GEN-15U | K+ channel (KvLQT1)                                         | 3016 | 2906A>G | 3     |

|          |          |        |         |                                                                                    |      |         |       |
|----------|----------|--------|---------|------------------------------------------------------------------------------------|------|---------|-------|
| AF000571 | AF000571 | 192500 | GEN-15U | K+ channel (KvLQT1)                                                                | 3073 | 2963A>G | 3     |
| AF001174 | AF001174 | 602898 | GEN-18T | Homo sapiens p38beta2 MAP kinase mRNA, complete cds                                | 1044 | 1038T>C | S     |
| AF004709 | AF004709 | 602899 | GEN-UX  | Homo sapiens stress-activated protein kinase 4 mRNA, complete cds                  | 432  | 384G>A  | S     |
| AF006689 | AF006689 | 603014 | GEN-YA  | Homo sapiens MAP kinase kinase Jnk2 mRNA, complete cds                             | 75   | (-1)G>A | 5     |
| AF009620 | AF009620 | 601763 | GEN-1HV | Homo sapiens apoptotic caspase Mch5-beta mRNA, alternatively spliced, complete cds | 808  | 808C>G  | H270D |
| AF009620 | AF009620 | 601763 | GEN-1HV | Homo sapiens apoptotic caspase Mch5-beta mRNA, alternatively spliced, complete cds | 915  | 915G>A  | S     |
| AF012535 | AF012535 | None   | GEN-1Z2 | Homo sapiens death receptor 5 (DR5) mRNA, complete cds                             | 234  | 95T>C   | L32P  |
| AF012535 | AF012535 | None   | GEN-1Z2 | Homo sapiens death receptor 5 (DR5) mRNA, complete cds                             | 339  | 200C>T  | A67V  |
| AF012535 | AF012535 | None   | GEN-1Z2 | Homo sapiens death receptor 5 (DR5) mRNA, complete cds                             | 1397 | 1258G>C | 3     |
| AF016709 | AF016709 | 602836 | GEN-1NE | PURINERGIC RECEPTOR P2X, LIGAND-GATED ION CHANNEL, 5; P2RX5                        | 1023 | 987T>C  | S     |
| AF016709 | AF016709 | 602836 | GEN-1NE | PURINERGIC RECEPTOR P2X, LIGAND-GATED ION CHANNEL, 5; P2RX5                        | 1025 | 989T>C  | F330S |
| AF016709 | AF016709 | 602836 | GEN-1NE | PURINERGIC RECEPTOR P2X, LIGAND-GATED ION CHANNEL, 5; P2RX5                        | 1090 | 1054G>C | E352Q |
| AF016709 | AF016709 | 602836 | GEN-1NE | PURINERGIC RECEPTOR P2X, LIGAND-GATED ION CHANNEL, 5; P2RX5                        | 1321 | 1285G>A | 3     |



|          |          |        |         |                                                                  |      |         |       |
|----------|----------|--------|---------|------------------------------------------------------------------|------|---------|-------|
| AF016709 | AF016709 | 602836 | GEN-1NE | PURINERGIC RECEPTOR P2X, LIGAND-GATED ION CHANNEL, 5; P2RX5      | 1424 | 1388C>G | 3     |
| AF016709 | AF016709 | 602836 | GEN-1NE | PURINERGIC RECEPTOR P2X, LIGAND-GATED ION CHANNEL, 5; P2RX5      | 1512 | 1476G>A | 3     |
| AF016709 | AF016709 | 602836 | GEN-1NE | PURINERGIC RECEPTOR P2X, LIGAND-GATED ION CHANNEL, 5; P2RX5      | 1743 | 1707A>G | 3     |
| AF016709 | AF016709 | 602836 | GEN-1NE | PURINERGIC RECEPTOR P2X, LIGAND-GATED ION CHANNEL, 5; P2RX5      | 1858 | 1822A>G | 3     |
| AF021792 | AF021792 | 603167 | GEN-2A5 | Homo sapiens Bcl-X/Bcl-2 binding protein (BAD) mRNA, partial cds | 781  | 781G>A  | 3     |
| AF021792 | AF021792 | 603167 | GEN-2A5 | Homo sapiens Bcl-X/Bcl-2 binding protein (BAD) mRNA, partial cds | 883  | 883C>A  | 3     |
| AF026070 | AF026070 | None   | GEN-26S | Homo sapiens death receptor 3 beta (DR3) mRNA, complete cds      | 455  | 387A>G  | S     |
| AF026070 | AF026070 | None   | GEN-26S | Homo sapiens death receptor 3 beta (DR3) mRNA, complete cds      | 1202 | 1134T>C | S     |
| AF026070 | AF026070 | None   | GEN-26S | Homo sapiens death receptor 3 beta (DR3) mRNA, complete cds      | 1204 | 1136T>G | L379R |
| AF026070 | AF026070 | None   | GEN-26S | Homo sapiens death receptor 3 beta (DR3) mRNA, complete cds      | 1237 | 1169A>G | H390R |
| HRH1     | AF026261 | 600167 | GEN-26W | Histamine receptor H1                                            | 1068 | 1068A>G | S     |
| AF029761 | AF029761 | None   | GEN-MND | Homo sapiens decoy receptor 2 mRNA, complete cds                 | 1011 | 929C>T  | S310L |
| ITGA7    | AF032108 | 600536 | GEN-2NO | Homo sapiens integrin alpha-7 mRNA, complete cds                 | 527  | 366G>A  | S     |
| TUBB     | AF035316 | 191130 | GEN-2IH | Homo sapiens clone 23678 mRNA, partial cds                       | 273  | 273G>A  | F     |
| TUBB     | AF035316 | 191130 | GEN-2IH | Homo sapiens clone 23678                                         | 295  | 295G>C  | A99P  |

|          |          |        |         |                                                                                                             |      |         |       |
|----------|----------|--------|---------|-------------------------------------------------------------------------------------------------------------|------|---------|-------|
| TUBB     | AF035316 | 191130 | GEN-2IH | Homo sapiens clone 23678 mRNA, partial cds                                                                  | 302  | 302C>T  | T101I |
| TUBB     | AF035316 | 191130 | GEN-2IH | Homo sapiens clone 23678 mRNA, partial cds                                                                  | 1059 | 1059G>A | 3     |
| AF039400 | AF039400 | 603906 | GEN-MQY | Homo sapiens calcium-dependent chloride channel-1 (hCLCA1) mRNA, complete cds                               | 2787 | 2436T>C | S     |
| AF043472 | AF043472 | 603888 | GEN-2XX | Homo sapiens Shab-related delayed-rectifier K <sup>+</sup> channel alpha subunit (KCNS3) mRNA, complete cds | 1840 | 1709T>G | 3     |
| AF048837 | AF048837 | 602973 | GEN-LGG | Homo sapiens cGMP-specific phosphodiesterase (PDE9A2) mRNA, complete cds                                    | 1551 | 1491T>C | S     |
| AF053712 | AF053712 | None   | GEN-MM2 | Homo sapiens osteoprotegerin ligand mRNA, complete cds                                                      | 2086 | 1902T>G | 3     |
| AF058921 | AF058921 | None   | GEN-LJY | Homo sapiens cytosolic phospholipase A2-gamma mRNA, complete cds                                            | 1972 | 1663G>A | 3     |
| AF058921 | AF058921 | None   | GEN-LJY | Homo sapiens cytosolic phospholipase A2-gamma mRNA, complete cds                                            | 1989 | 1680A>T | 3     |
| AF065164 | AF065164 | None   | GEN-LKQ | Homo sapiens hyperpolarization-activated channel 1 (IH1) mRNA, partial cds                                  | 1980 | 1860T>C | S     |
| AF094760 | AF094760 | None   | GEN-LSB | Homo sapiens RFXANK (RFXANK) mRNA, complete cds                                                             | 1038 | 621G>A  | S     |
| AF094760 | AF094760 | None   | GEN-LSB | Homo sapiens RFXANK (RFXANK) mRNA, complete cds                                                             | 1071 | 654C>T  | S     |
| D00017   | D00017   | 151740 | GEN-2D  | Lipocortin II (Annexin II)                                                                                  | 149  | 100G>A  | D34N  |
| D00017   | D00017   | 151740 | GEN-2D  | Lipocortin II (Annexin II)                                                                                  | 341  | 292G>T  | V98L  |
| D00017   | D00017   | 151740 | GEN-2D  | Lipocortin II (Annexin II)                                                                                  | 479  | 430A>T  | N144Y |

|         |        |        |         |                                                             |      |         |       |
|---------|--------|--------|---------|-------------------------------------------------------------|------|---------|-------|
| D00017  | D00017 | 151740 | GEN-2D  | Lipocortin II (Annexin II)                                  | 1288 | 1239G>A | 3     |
| D12614  | D12614 | 153440 | GEN-QD  | Human mRNA for lymphotoxin (TNF-beta), complete cds         | 319  | 179C>A  | T60N  |
| D13138  | D13138 | 179780 | GEN-1NW | Human mRNA for dipeptidase                                  | 566  | 523T>G  | S175A |
| CYP11B2 | D13752 | 124080 | GEN-CCD | Human CYP11B2 gene for steroid 18-hydroxylase, complete cds | 1600 | 1593G>A | 3     |
| D13811  | D13811 | 238310 | GEN-AA  | Glycine cleavage system: Protein T                          | 277  | 148G>T  | V50L  |
| D13811  | D13811 | 238310 | GEN-AA  | Glycine cleavage system: Protein T                          | 1073 | 944G>A  | R315K |
| D13811  | D13811 | 238310 | GEN-AA  | Glycine cleavage system: Protein T                          | 1083 | 954G>A  | S     |
| D13811  | D13811 | 238310 | GEN-AA  | Glycine cleavage system: Protein T                          | 1773 | 1644C>T | 3     |
| D13811  | D13811 | 238310 | GEN-AA  | Glycine cleavage system: Protein T                          | 2037 | 1908C>T | 3     |
| D25235  | D25235 | 104221 | GEN-3   | Adrenergic receptor alpha 1c                                | 1035 | 599T>G  | I200S |
| D25235  | D25235 | 104221 | GEN-3   | Adrenergic receptor alpha 1c                                | 1475 | 1039C>T | R347C |
| D25235  | D25235 | 104221 | GEN-3   | Adrenergic receptor alpha 1c                                | 1475 | 1039C>T | R347C |
| D25235  | D25235 | 104221 | GEN-3   | Adrenergic receptor alpha 1c                                | 2048 | 1612C>T | 3     |
| D25418  | D25418 | 600022 | GEN-78  | Prostaglandin I2 (prostaglandin) receptor (IP)              | 726  | 635G>A  | R212H |
| D25418  | D25418 | 600022 | GEN-78  | Prostaglandin I2 (prostaglandin) receptor (IP)              | 1047 | 956C>G  | S319W |
| D25418  | D25418 | 600022 | GEN-78  | Prostaglandin I2 (prostaglandin) receptor (IP)              | 1075 | 984A>C  | S     |
| D26579  | D26579 | 602267 | GEN-2B1 | Human mRNA for transmembrane protein, complete cds          | 709  | 700G>A  | D234N |
| D26579  | D26579 | 602267 | GEN-2B1 | Human mRNA for transmembrane protein, complete cds          | 909  | 900T>C  | S     |
| D26579  | D26579 | 602267 | GEN-2B1 | Human mRNA for transmembrane protein, complete cds          | 999  | 990C>T  | S     |

|        |        |        |         |                                                                              |      |          |       |
|--------|--------|--------|---------|------------------------------------------------------------------------------|------|----------|-------|
| D26579 | D26579 | 602267 | GEN-2B1 | complete cds<br>Human mRNA for transmembrane protein,                        | 1104 | 1095A>G  | S     |
| D32051 | D32051 | 138440 | GEN-4   | complete cds<br>Glycinamide ribonucleotide transformylase                    | 25   | (-47)G>A | 5     |
| D32051 | D32051 | 138440 | GEN-4   | Glycinamide ribonucleotide transformylase                                    | 1332 | 1261A>G  | I421V |
| D32051 | D32051 | 138440 | GEN-4   | Glycinamide ribonucleotide transformylase                                    | 1855 | 1784G>C  | 3     |
| PTGIR  | D38128 | 600022 | GEN-4DH | Human IP gene for prostacyclin receptor, exon 3                              | 203  | 204C>G   | 3     |
| PTGIR  | D38128 | 600022 | GEN-4DH | Human IP gene for prostacyclin receptor, exon 3                              | 231  | 232C>A   | 3     |
| D38145 | D38145 | 601699 | GEN-4E3 | Human mRNA for prostacyclin synthase, complete cds                           | 1646 | 1619T>C  | 3     |
| NT5    | D38524 | 129190 | GEN-2PF | Human mRNA for 5-nucleotidase                                                | 3075 | 2992C>T  | 3     |
| D42108 | D42108 | 600597 | GEN-2U4 | Phospholipase C epsilon                                                      | 1908 | 1705G>A  | V569I |
| D42108 | D42108 | 600597 | GEN-2U4 | Phospholipase C epsilon                                                      | 2864 | 2661G>A  | S     |
| D42108 | D42108 | 600597 | GEN-2U4 | Phospholipase C epsilon                                                      | 4453 | 4250G>A  | 3     |
| D45887 | D45887 | 114182 | GEN-BA  | Calmodulin 1 (phosphorylase kinase, delta)                                   | 34   | (-35)G>T | 5     |
| D49737 | D49737 | 602413 | GEN-2Z7 | Homo sapiens mRNA for cytochrome b large subunit of complex II, complete cds | 908  | 784G>A   | 3     |
| D86955 | D86955 | 601960 | GEN-41O | Human mRNA for CC chemokine LARC precursor, complete cds                     | 328  | 270T>C   | S     |
| D87461 | D87461 | 601931 | GEN-43N | Human mRNA for KIAA0271 gene, complete cds                                   | 2432 | 2256C>A  | 3     |
| D87845 | D87845 | 602344 | GEN-44C | Human mRNA for platelet-activating factor                                    | 2299 | 2096G>A  | 3     |

|        |        |        |         |                                                                           |      |            |   |
|--------|--------|--------|---------|---------------------------------------------------------------------------|------|------------|---|
| D87845 | D87845 | 602344 | GEN-44C | Human mRNA for platelet-activating factor acetylhydrolase 2, complete cds | 2332 | 2129A>G    | 3 |
| D89078 | D89078 | 601531 | GEN-7   | P2Y7 purinoceptor                                                         | 434  | (-1284)A>T | 5 |
| D89078 | D89078 | 601531 | GEN-7   | P2Y7 purinoceptor                                                         | 889  | (-829)G>C  | 5 |
| D89078 | D89078 | 601531 | GEN-7   | P2Y7 purinoceptor                                                         | 1156 | (-562)G>C  | 5 |
| D89078 | D89078 | 601531 | GEN-7   | P2Y7 purinoceptor                                                         | 2644 | 927T>C     | S |
| D89078 | D89078 | 601531 | GEN-7   | P2Y7 purinoceptor                                                         | 2920 | 1203A>G    | 3 |
| EDNRA  | D90348 | 131243 | GEN-4DX | Endothelin Receptor Type A                                                | 1449 | 969C>T     | S |
| EDNRA  | D90348 | 131243 | GEN-4DX | Endothelin Receptor Type A                                                | 1449 | 969C>T     | S |
| EDNRA  | D90348 | 131243 | GEN-4DX | Endothelin Receptor Type A                                                | 1485 | 1005A>G    | S |
| EDNRA  | D90348 | 131243 | GEN-4DX | Endothelin Receptor Type A                                                | 1485 | 1005A>G    | S |
| EDNRA  | D90348 | 131243 | GEN-4DX | Endothelin Receptor Type A                                                | 1834 | 1354C>G    | 3 |
| EDNRA  | D90348 | 131243 | GEN-4DX | Endothelin Receptor Type A                                                | 1834 | 1354C>G    | 3 |
| EDNRA  | D90348 | 131243 | GEN-4DX | Endothelin Receptor Type A                                                | 2228 | 1748G>A    | 3 |
| EDNRA  | D90348 | 131243 | GEN-4DX | Endothelin Receptor Type A                                                | 2376 | 1896G>A    | 3 |
| EDNRA  | D90348 | 131243 | GEN-4DX | Endothelin Receptor Type A                                                | 2764 | 2284G>A    | 3 |
| EDNRA  | D90348 | 131243 | GEN-4DX | Endothelin Receptor Type A                                                | 2764 | 2284G>A    | 3 |
| EDNRA  | D90348 | 131243 | GEN-4DX | Endothelin Receptor Type A                                                | 2840 | 2360G>C    | 3 |
| EDNRA  | D90348 | 131243 | GEN-4DX | Endothelin Receptor Type A                                                | 2935 | 2455G>A    | 3 |
| EDNRA  | D90348 | 131243 | GEN-4DX | Endothelin Receptor Type A                                                | 3294 | 2814A>G    | 3 |
| J00123 | J00123 | 131330 | GEN-MK4 | Human enkephalin gene                                                     | 81   | 81C>T      | S |
| DHFR   | J00140 | 126060 | GEN-    | Human dihydrofolate                                                       | 721  | 679T>A     | 3 |

|        |        |        |                |                                                                           |      |          |       |
|--------|--------|--------|----------------|---------------------------------------------------------------------------|------|----------|-------|
| DHFR   | J00140 | 126060 | 4E9<br>GEN-4E9 | reductase gene<br>Human dihydrofolate reductase gene                      | 721  | 679T>A   | 3     |
| DHFR   | J00140 | 126060 | GEN-4E9        | Human dihydrofolate reductase gene                                        | 829  | 787C>T   | 3     |
| CBG    | J02943 | 122500 | GEN-Y2         | Human corticosteroid binding globulin mRNA, complete cds                  | 106  | 71A>T    | D24V  |
| CBG    | J02943 | 122500 | GEN-Y2         | Human corticosteroid binding globulin mRNA, complete cds                  | 971  | 936T>C   | S     |
| CBG    | J02943 | 122500 | GEN-Y2         | Human corticosteroid binding globulin mRNA, complete cds                  | 1229 | 1194G>A  | S     |
| J03004 | J03004 | 139360 | GEN-79         | Guanine nucleotide binding protein (G protein), alpha inhibiting activity | 758  | 681C>T   | S     |
| J03019 | J03019 | 109630 | GEN-4D6        | polypeptide 2<br>Human beta-1-adrenergic receptor mRNA, complete cds      | 503  | 417G>A   | S     |
| J03143 | J03143 | 107470 | GEN-ZK         | Human interferon-gamma receptor mRNA, complete cds                        | 1098 | 1050T>G  | S     |
| J03209 | J03209 | 185250 | GEN-PK         | Human matrix metalloproteinase-3 (MMP-3) mRNA, complete cds               | 133  | 133G>A   | E45K  |
| J03209 | J03209 | 185250 | GEN-PK         | Human matrix metalloproteinase-3 (MMP-3) mRNA, complete cds               | 288  | 288C>T   | S     |
| J03210 | J03210 | 120360 | GEN-ZY         | Human collagenase type IV mRNA, 3 end                                     | 721  | 721C>T   | P241S |
| J03210 | J03210 | 120360 | GEN-ZY         | Human collagenase type IV mRNA, 3 end                                     | 1759 | 1759C>T  | P587S |
| J03250 | J03250 | 172420 | GEN-C4         | DNA topoisomerase I                                                       | 160  | (-52)C>T | 5     |
| J03250 | J03250 | 172420 | GEN-C4         | DNA topoisomerase I                                                       | 590  | 379G>A   | V127I |
| J03250 | J03250 | 172420 | GEN-C4         | DNA topoisomerase I                                                       | 1984 | 1773G>A  | S     |
| J03258 | J03258 | 601769 | GEN-2J         | Vitamin D (1,25-dihydroxyvitamin D3) receptor                             | 172  | 57C>T    | S     |

|        |        |        |         |                                                          |      |          |       |
|--------|--------|--------|---------|----------------------------------------------------------|------|----------|-------|
| J03258 | J03258 | 601769 | GEN-2J  | Vitamin D (1,25-dihydroxyvitamin D3) receptor            | 559  | 444C>T   | S     |
| J03258 | J03258 | 601769 | GEN-2J  | Vitamin D (1,25-dihydroxyvitamin D3) receptor            | 1704 | 1589C>A  | 3     |
| J03258 | J03258 | 601769 | GEN-2J  | Vitamin D (1,25-dihydroxyvitamin D3) receptor            | 1833 | 1718C>G  | 3     |
| J03258 | J03258 | 601769 | GEN-2J  | Vitamin D (1,25-dihydroxyvitamin D3) receptor            | 1858 | 1743G>T  | 3     |
| J03258 | J03258 | 601769 | GEN-2J  | Vitamin D (1,25-dihydroxyvitamin D3) receptor            | 1959 | 1844A>C  | 3     |
| J03258 | J03258 | 601769 | GEN-2J  | Vitamin D (1,25-dihydroxyvitamin D3) receptor            | 2190 | 2075delT | F     |
| J03258 | J03258 | 601769 | GEN-2J  | Vitamin D (1,25-dihydroxyvitamin D3) receptor            | 3301 | 3186C>A  | 3     |
| J03258 | J03258 | 601769 | GEN-2J  | Vitamin D (1,25-dihydroxyvitamin D3) receptor            | 3991 | 3876A>G  | 3     |
| J03258 | J03258 | 601769 | GEN-2J  | Vitamin D (1,25-dihydroxyvitamin D3) receptor            | 4187 | 4072G>A  | 3     |
| J03258 | J03258 | 601769 | GEN-2J  | Vitamin D (1,25-dihydroxyvitamin D3) receptor            | 4187 | 4072G>A  | 3     |
| J03459 | J03459 | 151570 | GEN-8   | Leukotriene A4 hydrolase                                 | 140  | 72G>T    | S     |
| J03459 | J03459 | 151570 | GEN-8   | Leukotriene A4 hydrolase                                 | 1511 | 1443A>T  | E481D |
| C7     | J03507 | 217070 | GEN-11R | Human complement protein component C7 mRNA, complete cds | 1951 | 1951G>A  | V651I |
| C7     | J03507 | 217070 | GEN-11R | Human complement protein component C7 mRNA, complete cds | 3032 | 3032T>C  | 3     |
| C7     | J03507 | 217070 | GEN-11R | Human complement protein component C7 mRNA, complete cds | 3634 | 3634A>G  | 3     |

|        |        |        |         |                                                                                                                                    |      |                |       |
|--------|--------|--------|---------|------------------------------------------------------------------------------------------------------------------------------------|------|----------------|-------|
| C7     | J03507 | 217070 | GEN-11R | Human complement protein component C7 mRNA, complete cds                                                                           | 3831 | 3831A>G        | 3     |
| J03571 | J03571 | 152390 | GEN-9   | Lipoxygenases: 5-lipoxygenase (leukocytes)                                                                                         | 55   | 21C>T          | S     |
| J03571 | J03571 | 152390 | GEN-9   | Lipoxygenases: 5-lipoxygenase (leukocytes)                                                                                         | 304  | 270G>A         | S     |
| J03571 | J03571 | 152390 | GEN-9   | Lipoxygenases: 5-lipoxygenase (leukocytes)                                                                                         | 304  | 270G>A         | S     |
| J03571 | J03571 | 152390 | GEN-9   | Lipoxygenases: 5-lipoxygenase (leukocytes)                                                                                         | 959  | 925C>A         | P309T |
| J03571 | J03571 | 152390 | GEN-9   | Lipoxygenases: 5-lipoxygenase (leukocytes)                                                                                         | 1762 | 1728A>T        | S     |
| J03571 | J03571 | 152390 | GEN-9   | Lipoxygenases: 5-lipoxygenase (leukocytes)                                                                                         | 2076 | 2042-2043AC>AC | 3     |
| J03571 | J03571 | 152390 | GEN-9   | Lipoxygenases: 5-lipoxygenase (leukocytes)                                                                                         | 2076 | 2042-2043delAC | F     |
| J03571 | J03571 | 152390 | GEN-9   | Lipoxygenases: 5-lipoxygenase (leukocytes)                                                                                         | 2328 | 2294C>T        | 3     |
| J03571 | J03571 | 152390 | GEN-9   | Lipoxygenases: 5-lipoxygenase (leukocytes)                                                                                         | 2376 | 2342T>G        | 3     |
| PTHLH  | J03580 | 168470 | GEN-11U | Lipoxygenase (leukocytes) Human, parathyroid-like protein (associated with humoral hypercalcemia of malignancy) mRNA, complete cds | 975  | 37G>A          | V13M  |
| PTHLH  | J03580 | 168470 | GEN-11U | Human, parathyroid-like protein (associated with humoral hypercalcemia of malignancy) mRNA, complete cds                           | 996  | 58G>A          | V20M  |
| J03853 | J03853 | 104250 | GEN-A   | Adrenergic receptor alpha 2c                                                                                                       | 1202 | 1164C>T        | S     |
| J03853 | J03853 | 104250 | GEN-A   | Adrenergic receptor alpha 2c                                                                                                       | 1237 | 1199T>G        | I400S |
| J03853 | J03853 | 104250 | GEN-A   | Adrenergic receptor alpha 2c                                                                                                       | 1372 | 1334C>G        | P445R |
| J03853 | J03853 | 104250 | GEN-A   | Adrenergic receptor alpha 2c                                                                                                       | 1379 | 1341C>T        | S     |
| J04031 | J04031 | 172460 | GEN-CB  | Methylenetetrahydrofolate cyclohydrolase                                                                                           | 454  | 401G>A         | R134K |



|        |        |        |             |                                                           |      |         |        |
|--------|--------|--------|-------------|-----------------------------------------------------------|------|---------|--------|
| J04031 | J04031 | 172460 | GEN-CB      | Methenyltetrahydrofolate<br>cyclohydrolase                | 969  | 916C>G  | Q306E  |
| J04031 | J04031 | 172460 | GEN-CB      | Methenyltetrahydrofolate<br>cyclohydrolase                | 1614 | 1561T>C | S      |
| J04031 | J04031 | 172460 | GEN-CB      | Methenyltetrahydrofolate<br>cyclohydrolase                | 2011 | 1958G>A | R653Q  |
| J04031 | J04031 | 172460 | GEN-CB      | Methenyltetrahydrofolate<br>cyclohydrolase                | 2335 | 2282C>T | T761M  |
| J04046 | J04046 | 114183 | GEN-<br>13N | Human calmodulin mRNA,<br>complete cds                    | 791  | 688C>T  | 3      |
| J04046 | J04046 | 114183 | GEN-<br>13N | Human calmodulin mRNA,<br>complete cds                    | 881  | 778T>C  | 3      |
| J04046 | J04046 | 114183 | GEN-<br>13N | Human calmodulin mRNA,<br>complete cds                    | 1927 | 1824T>C | 3      |
| C1S    | J04080 | 120580 | GEN-<br>13T | Complement C1S<br>component precursor (C1<br>esterase)    | 558  | 356G>A  | R119H  |
| C1S    | J04080 | 120580 | GEN-<br>13T | Complement C1S<br>component precursor (C1<br>esterase)    | 2140 | 1938A>T | K646N  |
| C1S    | J04080 | 120580 | GEN-<br>13T | Complement C1S<br>component precursor (C1<br>esterase)    | 2234 | 2032A>T | T678S  |
| C1S    | J04080 | 120580 | GEN-<br>13T | Complement C1S<br>component precursor (C1<br>esterase)    | 2333 | 2131G>T | 3      |
| J04132 | J04132 | 186780 | GEN-<br>KXY | Human T cell receptor<br>zeta-chain mRNA,<br>complete cds | 1403 | 1329G>C | 3      |
| J04132 | J04132 | 186780 | GEN-<br>KXY | Human T cell receptor<br>zeta-chain mRNA,<br>complete cds | 1410 | 1336A>T | 3      |
| J04145 | J04145 | 120980 | GEN-B       | Leukocyte integrin alpha-m                                | 206  | 206G>A  | R69H   |
| J04145 | J04145 | 120980 | GEN-B       | Leukocyte integrin alpha-m                                | 1780 | 1780C>T | S      |
| J04145 | J04145 | 120980 | GEN-B       | Leukocyte integrin alpha-m                                | 2478 | 2478G>A | S      |
| J04145 | J04145 | 120980 | GEN-B       | Leukocyte integrin alpha-m                                | 2978 | 2978C>A | T993N  |
| J04145 | J04145 | 120980 | GEN-B       | Leukocyte integrin alpha-m                                | 3415 | 3415C>T | P1139S |
| J04145 | J04145 | 120980 | GEN-B       | Leukocyte integrin alpha-m                                | 3661 | 3661C>T | 3      |
| J04145 | J04145 | 120980 | GEN-B       | Leukocyte integrin alpha-m                                | 3804 | 3804A>G | 3      |
| J04145 | J04145 | 120980 | GEN-B       | Leukocyte integrin alpha-m                                | 4071 | 4071G>A | 3      |

|        |        |        |         |                                                                             |      |         |       |
|--------|--------|--------|---------|-----------------------------------------------------------------------------|------|---------|-------|
| SPN    | J04168 | 182160 | GEN-13W | Human leukosialin mRNA, complete cds                                        | 974  | 879C>T  | S     |
| SPN    | J04168 | 182160 | GEN-13W | Human leukosialin mRNA, complete cds                                        | 1328 | 1233G>C | 3     |
| J04208 | J04208 | 146691 | GEN-2M  | IMP (inosine monophosphate) dehydrogenase 2                                 | 349  | 302C>G  | A101G |
| J04208 | J04208 | 146691 | GEN-2M  | IMP (inosine monophosphate) dehydrogenase 2                                 | 1570 | 1523C>T | S508L |
| G22P1  | J04611 | 152690 | GEN-153 | Human lupus p70 (Ku) autoantigen protein mRNA, complete cds                 | 1762 | 1729A>T | T577S |
| G22P1  | J04611 | 152690 | GEN-153 | Human lupus p70 (Ku) autoantigen protein mRNA, complete cds                 | 1812 | 1779T>G | S     |
| G22P1  | J04611 | 152690 | GEN-153 | Human lupus p70 (Ku) autoantigen protein mRNA, complete cds                 | 1900 | 1867G>T | 3     |
| BPI    | J04739 | 109195 | GEN-15B | Human bactericidal permeability increasing protein (BPI) mRNA, complete cds | 1525 | 1495G>A | 3     |
| C6     | J05064 | 217050 | GEN-16S | Human complement component C6 mRNA, complete cds                            | 3281 | 3126G>A | 3     |
| J05480 | J05480 | 114105 | GEN-D   | Calcineurin A                                                               | 834  | 834A>G  | 3     |
| J05594 | J05594 | 601688 | GEN-E   | Prostaglandin 15-OH dehydrogenase (PGDH)                                    | 173  | 156A>G  | S     |
| J05594 | J05594 | 601688 | GEN-E   | Prostaglandin 15-OH dehydrogenase (PGDH)                                    | 913  | 896C>G  | 3     |
| J05594 | J05594 | 601688 | GEN-E   | Prostaglandin 15-OH dehydrogenase (PGDH)                                    | 950  | 933G>A  | 3     |
| J05594 | J05594 | 601688 | GEN-E   | Prostaglandin 15-OH dehydrogenase (PGDH)                                    | 1448 | 1431G>A | 3     |
| J05594 | J05594 | 601688 | GEN-E   | Prostaglandin 15-OH dehydrogenase (PGDH)                                    | 1972 | 1955T>C | 3     |
| J05594 | J05594 | 601688 | GEN-E   | Prostaglandin 15-OH dehydrogenase (PGDH)                                    | 1972 | 1955T>C | 3     |
| K00396 | K00396 | 107741 | GEN-P0  | Human apolipoprotein E (epsilon 2 and 3 alleles)                            | 112  | 52G>A   | A18T  |

|        |        |        |        |                                                             |     |         |       |
|--------|--------|--------|--------|-------------------------------------------------------------|-----|---------|-------|
| K00396 | K00396 | 107741 | GEN-P0 | Human apolipoprotein E<br>(epsilon 2 and 3 alleles)<br>mRNA | 121 | 61G>A   | E21K  |
| K00396 | K00396 | 107741 | GEN-P0 | Human apolipoprotein E<br>(epsilon 2 and 3 alleles)<br>mRNA | 151 | 91G>A   | E31K  |
| K00396 | K00396 | 107741 | GEN-P0 | Human apolipoprotein E<br>(epsilon 2 and 3 alleles)<br>mRNA | 197 | 137T>C  | L46P  |
| K00396 | K00396 | 107741 | GEN-P0 | Human apolipoprotein E<br>(epsilon 2 and 3 alleles)<br>mRNA | 204 | 144delG | F     |
| K00396 | K00396 | 107741 | GEN-P0 | Human apolipoprotein E<br>(epsilon 2 and 3 alleles)<br>mRNA | 238 | 178A>G  | T60A  |
| K00396 | K00396 | 107741 | GEN-P0 | Human apolipoprotein E<br>(epsilon 2 and 3 alleles)<br>mRNA | 365 | 305C>G  | P102R |
| K00396 | K00396 | 107741 | GEN-P0 | Human apolipoprotein E<br>(epsilon 2 and 3 alleles)<br>mRNA | 409 | 349G>A  | A117T |
| K00396 | K00396 | 107741 | GEN-P0 | Human apolipoprotein E<br>(epsilon 2 and 3 alleles)<br>mRNA | 448 | 388T>C  | C130R |
| K00396 | K00396 | 107741 | GEN-P0 | Human apolipoprotein E<br>(epsilon 2 and 3 alleles)<br>mRNA | 494 | 434G>A  | G145D |
| K00396 | K00396 | 107741 | GEN-P0 | Human apolipoprotein E<br>(epsilon 2 and 3 alleles)<br>mRNA | 515 | 455G>A  | R152Q |
| K00396 | K00396 | 107741 | GEN-P0 | Human apolipoprotein E<br>(epsilon 2 and 3 alleles)<br>mRNA | 520 | 460C>A  | R154S |
| K00396 | K00396 | 107741 | GEN-P0 | Human apolipoprotein E<br>(epsilon 2 and 3 alleles)<br>mRNA | 538 | 478C>T  | R160C |
| K00396 | K00396 | 107741 | GEN-P0 | Human apolipoprotein E<br>(epsilon 2 and 3 alleles)<br>mRNA | 547 | 487C>T  | R163C |
| K00396 | K00396 | 107741 | GEN-P0 | Human apolipoprotein E<br>(epsilon 2 and 3 alleles)<br>mRNA | 548 | 488G>A  | R163H |

|        |        |        |        |                                                             |      |        |       |
|--------|--------|--------|--------|-------------------------------------------------------------|------|--------|-------|
| K00396 | K00396 | 107741 | GEN-P0 | (epsilon 2 and 3 alleles)<br>mRNA                           | 550  | 490A>G | K164E |
| K00396 | K00396 | 107741 | GEN-P0 | Human apolipoprotein E<br>(epsilon 2 and 3 alleles)<br>mRNA | 586  | 528C>T | R176C |
| K00396 | K00396 | 107741 | GEN-P0 | Human apolipoprotein E<br>(epsilon 2 and 3 alleles)<br>mRNA | 586  | 526C>T | R176C |
| K00396 | K00396 | 107741 | GEN-P0 | Human apolipoprotein E<br>(epsilon 2 and 3 alleles)<br>mRNA | 743  | 683G>A | F     |
| K00396 | K00396 | 107741 | GEN-P0 | Human apolipoprotein E<br>(epsilon 2 and 3 alleles)<br>mRNA | 785  | 725G>A | R242Q |
| K00396 | K00396 | 107741 | GEN-P0 | Human apolipoprotein E<br>(epsilon 2 and 3 alleles)<br>mRNA | 796  | 736C>T | R246C |
| K00396 | K00396 | 107741 | GEN-P0 | Human apolipoprotein E<br>(epsilon 2 and 3 alleles)<br>mRNA | 821  | 761T>A | V254E |
| K00396 | K00396 | 107741 | GEN-P0 | Human apolipoprotein E<br>(epsilon 2 and 3 alleles)<br>mRNA | 865  | 805C>G | R269G |
| K00396 | K00396 | 107741 | GEN-P0 | Human apolipoprotein E<br>(epsilon 2 and 3 alleles)<br>mRNA | 935  | 875G>A | R292H |
| K00396 | K00396 | 107741 | GEN-P0 | Human apolipoprotein E<br>(epsilon 2 and 3 alleles)<br>mRNA | 1000 | 940A>C | S314R |
| K01171 | K01171 | None   | GEN-PB | Human HLA-DR alpha-<br>chain mRNA                           | 297  | 283T>C | S     |
| K01171 | K01171 | None   | GEN-PB | Human HLA-DR alpha-<br>chain mRNA                           | 416  | 402C>A | S     |
| K01171 | K01171 | None   | GEN-PB | Human HLA-DR alpha-<br>chain mRNA                           | 665  | 651C>T | S     |
| K01171 | K01171 | None   | GEN-PB | Human HLA-DR alpha-<br>chain mRNA                           | 738  | 724G>T | V242L |
| K01171 | K01171 | None   | GEN-PB | Human HLA-DR alpha-<br>chain mRNA                           | 748  | 734G>A | S245N |

|        |        |        |        |                                                                           |      |         |       |
|--------|--------|--------|--------|---------------------------------------------------------------------------|------|---------|-------|
| K01171 | K01171 | None   | GEN-PB | Human HLA-DR alpha-chain mRNA                                             | 797  | 783A>G  | 3     |
| K01171 | K01171 | None   | GEN-PB | Human HLA-DR alpha-chain mRNA                                             | 842  | 828A>G  | 3     |
| K01171 | K01171 | None   | GEN-PB | Human HLA-DR alpha-chain mRNA                                             | 901  | 887G>A  | 3     |
| K01171 | K01171 | None   | GEN-PB | Human HLA-DR alpha-chain mRNA                                             | 928  | 914T>A  | 3     |
| K01171 | K01171 | None   | GEN-PB | Human HLA-DR alpha-chain mRNA                                             | 933  | 919T>A  | 3     |
| K01171 | K01171 | None   | GEN-PB | Human HLA-DR alpha-chain mRNA                                             | 942  | 928C>T  | 3     |
| K01171 | K01171 | None   | GEN-PB | Human HLA-DR alpha-chain mRNA                                             | 954  | 940G>A  | 3     |
| K01171 | K01171 | None   | GEN-PB | Human HLA-DR alpha-chain mRNA                                             | 999  | 985T>G  | 3     |
| K01171 | K01171 | None   | GEN-PB | Human HLA-DR alpha-chain mRNA                                             | 1035 | 1021A>C | 3     |
| K01171 | K01171 | None   | GEN-PB | Human HLA-DR alpha-chain mRNA                                             | 1077 | 1063C>T | 3     |
| K01171 | K01171 | None   | GEN-PB | Human HLA-DR alpha-chain mRNA                                             | 1091 | 1077C>G | 3     |
| K01171 | K01171 | None   | GEN-PB | Human HLA-DR alpha-chain mRNA                                             | 1154 | 1140A>C | 3     |
| K01171 | K01171 | None   | GEN-PB | Human HLA-DR alpha-chain mRNA                                             | 1171 | 1157T>A | 3     |
| KNG    | K02566 | 228960 | GEN-X2 | Human alpha-2-thiol proteinase inhibitor mRNA, complete coding sequence   | 1248 | 1199C>A | T400K |
| K02765 | K02765 | 120700 | GEN-XM | Human complement component C3 mRNA, alpha and beta subunits, complete cds | 1001 | 941T>C  | L314P |
| K02765 | K02765 | 120700 | GEN-XM | Human complement component C3 mRNA, alpha and beta subunits, complete cds | 2575 | 2515G>A | V839I |
| K02765 | K02765 | 120700 | GEN-XM | Human complement component C3 mRNA, alpha and beta subunits, complete cds | 3108 | 3048C>T | S     |

|        |        |        |         |                                                                                               |      |                          |                        |
|--------|--------|--------|---------|-----------------------------------------------------------------------------------------------|------|--------------------------|------------------------|
| K02765 | K02765 | 120700 | GEN-XM  | complete cds                                                                                  | 3561 | 3501C>G                  | S                      |
|        |        |        |         | Human complement component C3 mRNA, alpha and beta subunits, complete cds                     |      |                          |                        |
| K02765 | K02765 | 120700 | GEN-XM  | Human complement component C3 mRNA, alpha and beta subunits, complete cds                     | 4371 | 4311C>T                  | S                      |
| K02765 | K02765 | 120700 | GEN-XM  | Human complement component C3 mRNA, alpha and beta subunits, complete cds                     | 4544 | 4484C>A                  | P1495Q                 |
| K02765 | K02765 | 120700 | GEN-XM  | Human complement component C3 mRNA, alpha and beta subunits, complete cds                     | 4938 | 4878T>C                  | S                      |
| K02765 | K02765 | 120700 | GEN-XM  | Human complement component C3 mRNA, alpha and beta subunits, complete cds                     | 4956 | 4896T>C                  | S                      |
| K02770 | K02770 | 147720 | GEN-5M  | Interleukin 1, beta                                                                           | 19   | (-68)A>C                 | 5                      |
| K02770 | K02770 | 147720 | GEN-5M  | Interleukin 1, beta                                                                           | 26   | (-61)A>C                 | 5                      |
| K02770 | K02770 | 147720 | GEN-5M  | Interleukin 1, beta                                                                           | 48   | (-39)C>T                 | 5                      |
| K02770 | K02770 | 147720 | GEN-5M  | Interleukin 1, beta                                                                           | 114  | 28G>A                    | E10K                   |
| K02770 | K02770 | 147720 | GEN-5M  | Interleukin 1, beta                                                                           | 119  | 33G>A                    | M11I                   |
| L01087 | L01087 | 600448 | GEN-CM  | Protein kinase C-theta                                                                        | 1940 | 1846C>A                  | S                      |
| L01087 | L01087 | 600448 | GEN-CM  | Protein kinase C-theta                                                                        | 1943 | 1849G>A                  | E617K                  |
| L04270 | L04270 | 600979 | GEN-144 | Homo sapiens (clone CD18) tumor necrosis factor receptor 2 related protein mRNA, complete cds | 1478 | 1310G>T                  | 3                      |
| L05148 | L05148 | 176947 | GEN-KYC | Human protein tyrosine kinase related mRNA sequence                                           | 1886 | 1887G>A                  | 3                      |
| L05597 | L05597 | None   | GEN-4EV | Serotonin 5-HT receptors 5-HT1F                                                               | 824  | 600T>C                   | S                      |
| L05597 | L05597 | None   | GEN-4EV | Serotonin 5-HT receptors 5-HT1F                                                               | 1010 | 786^787insA<br>ATAAAATTC | [H262Q;26<br>2^263insl |

|        |        |        |         |                                                                                       |      |                 |           |
|--------|--------|--------|---------|---------------------------------------------------------------------------------------|------|-----------------|-----------|
| EDNRB  | L06623 | 131244 | GEN-19S | Endothelin Receptor Type B                                                            | 88   | AT<br>(-146)A>G | KFIJ<br>5 |
| EDNRB  | L06623 | 131244 | GEN-19S | Endothelin Receptor Type B                                                            | 332  | 99C>T           | S         |
| EDNRB  | L06623 | 131244 | GEN-19S | Endothelin Receptor Type B                                                            | 1064 | 831G>A          | S         |
| EDNRB  | L06623 | 131244 | GEN-19S | Endothelin Receptor Type B                                                            | 1064 | 831G>A          | S         |
| TGFBR3 | L07594 | 600742 | GEN-1EA | Human transforming growth factor-beta type III receptor (TGF-beta) mRNA, complete cds | 3966 | 3618G>C         | 3         |
| L07861 | L07861 | 176977 | GEN-D0  | Protein kinase C, delta                                                               | 445  | 387G>A          | S         |
| L07861 | L07861 | 176977 | GEN-D0  | Protein kinase C, delta                                                               | 1835 | 1777G>A         | V593M     |
| CCKBR  | L08112 | 118445 | GEN-1FL | Cholecystokinin (CCKb)                                                                | 456  | 456G>A          | S         |
| MIF    | L10612 | 153620 | GEN-1J8 | Human glycosylation-inhibiting factor mRNA, complete cds                              | 170  | 96C>G           | S         |
| MIF    | L10612 | 153620 | GEN-1J8 | Human glycosylation-inhibiting factor mRNA, complete cds                              | 221  | 147C>G          | S         |
| MIF    | L10612 | 153620 | GEN-1J8 | Human glycosylation-inhibiting factor mRNA, complete cds                              | 227  | 153C>G          | S         |
| MIF    | L10612 | 153620 | GEN-1J8 | Human glycosylation-inhibiting factor mRNA, complete cds                              | 239  | 165G>A          | S         |
| MIF    | L10612 | 153620 | GEN-1J8 | Human glycosylation-inhibiting factor mRNA, complete cds                              | 329  | 255C>A          | S         |
| MIF    | L10612 | 153620 | GEN-1J8 | Human glycosylation-inhibiting factor mRNA, complete cds                              | 445  | 371C>T          | 3         |
| L10717 | L10717 | 186973 | GEN-1JB | Homo sapiens T cell-specific tyrosine kinase mRNA, complete cds                       | 856  | (-1168)G>A      | 5         |
| L10717 | L10717 | 186973 | GEN-1JB | Homo sapiens T cell-specific tyrosine kinase mRNA, complete cds                       | 1472 | (-552)G>A       | 5         |

|        |        |        |         |                                                                 |      |         |       |
|--------|--------|--------|---------|-----------------------------------------------------------------|------|---------|-------|
| L10717 | L10717 | 186973 | GEN-1JB | Homo sapiens T cell-specific tyrosine kinase mRNA, complete cds | 4897 | 2874G>A | 3     |
| L10717 | L10717 | 186973 | GEN-1JB | Homo sapiens T cell-specific tyrosine kinase mRNA, complete cds | 5625 | 3602G>C | 3     |
| L10717 | L10717 | 186973 | GEN-1JB | Homo sapiens T cell-specific tyrosine kinase mRNA, complete cds | 5628 | 3605A>C | 3     |
| L10819 | L10819 | 171150 | GEN-LVD | Homo sapiens aryl sulfotransferase mRNA, complete cds           | 191  | 153C>T  | S     |
| L10819 | L10819 | 171150 | GEN-LVD | Homo sapiens aryl sulfotransferase mRNA, complete cds           | 200  | 162G>A  | S     |
| L10819 | L10819 | 171150 | GEN-LVD | Homo sapiens aryl sulfotransferase mRNA, complete cds           | 230  | 192T>C  | S     |
| L10819 | L10819 | 171150 | GEN-LVD | Homo sapiens aryl sulfotransferase mRNA, complete cds           | 242  | 204G>A  | S     |
| L10819 | L10819 | 171150 | GEN-LVD | Homo sapiens aryl sulfotransferase mRNA, complete cds           | 295  | 257C>T  | A86V  |
| L10819 | L10819 | 171150 | GEN-LVD | Homo sapiens aryl sulfotransferase mRNA, complete cds           | 330  | 292G>A  | D98N  |
| L10819 | L10819 | 171150 | GEN-LVD | Homo sapiens aryl sulfotransferase mRNA, complete cds           | 338  | 300G>A  | S     |
| L10819 | L10819 | 171150 | GEN-LVD | Homo sapiens aryl sulfotransferase mRNA, complete cds           | 638  | 600C>G  | S     |
| L10819 | L10819 | 171150 | GEN-LVD | Homo sapiens aryl sulfotransferase mRNA, complete cds           | 676  | 638A>G  | H213R |
| L10819 | L10819 | 171150 | GEN-LVD | Homo sapiens aryl sulfotransferase mRNA, complete cds           | 940  | 902G>A  | 3     |
| L10819 | L10819 | 171150 | GEN-LVD | Homo sapiens aryl sulfotransferase mRNA, complete cds           | 1011 | 973T>C  | 3     |



|        |        |        |         |                                                                     |      |         |   |
|--------|--------|--------|---------|---------------------------------------------------------------------|------|---------|---|
| L11005 | L11005 | 602841 | GEN-1JU | complete cds<br>Human aldehyde oxidase (hAOX) mRNA, complete cds    | 4284 | 4154C>A | 3 |
| L11005 | L11005 | 602841 | GEN-1JU | Human aldehyde oxidase (hAOX) mRNA, complete cds                    | 4447 | 4317G>C | 3 |
| L11005 | L11005 | 602841 | GEN-1JU | Human aldehyde oxidase (hAOX) mRNA, complete cds                    | 4525 | 4395T>G | 3 |
| L11005 | L11005 | 602841 | GEN-1JU | Human aldehyde oxidase (hAOX) mRNA, complete cds                    | 4675 | 4545G>A | 3 |
| C4BPB  | L11244 | 120831 | GEN-1K2 | Human (clone A12) C4b-binding protein beta-chain mRNA, complete cds | 538  | 204G>A  | S |
| C4BPB  | L11244 | 120831 | GEN-1K2 | Human (clone A12) C4b-binding protein beta-chain mRNA, complete cds | 796  | 462C>T  | S |
| C4BPB  | L11244 | 120831 | GEN-1K2 | Human (clone A12) C4b-binding protein beta-chain mRNA, complete cds | 958  | 624C>A  | S |
| L11284 | L11284 | 176872 | GEN-1K8 | Homosapiens ERK activator kinase (MEK1) mRNA                        | 1763 | 1764T>C | 3 |
| L11284 | L11284 | 176872 | GEN-1K8 | Homosapiens ERK activator kinase (MEK1) mRNA                        | 1914 | 1915G>A | 3 |
| L11285 | L11285 | 601263 | GEN-1K7 | Homosapiens ERK activator kinase (MEK2) mRNA                        | 252  | 253C>A  | 3 |
| L11285 | L11285 | 601263 | GEN-1K7 | Homosapiens ERK activator kinase (MEK2) mRNA                        | 276  | 277T>C  | 3 |
| L11285 | L11285 | 601263 | GEN-1K7 | Homosapiens ERK activator kinase (MEK2) mRNA                        | 537  | 538C>T  | 3 |
| L11285 | L11285 | 601263 | GEN-1K7 | Homosapiens ERK activator kinase (MEK2) mRNA                        | 613  | 614G>C  | 3 |
| L11285 | L11285 | 601263 | GEN-    | Homosapiens ERK activator kinase (MEK2) mRNA                        | 744  | 745A>C  | 3 |

|        |        |        |         |         |                                                                                      |      |         |       |
|--------|--------|--------|---------|---------|--------------------------------------------------------------------------------------|------|---------|-------|
| L11285 | L11285 | 601263 | GEN-1K7 | 1K7     | activator kinase (MEK2) mRNA                                                         | 1156 | 1157G>T | 3     |
| L11285 | L11285 | 601263 | GEN-1K7 | GEN-1K7 | Homosapiens ERK activator kinase (MEK2) mRNA                                         | 1311 | 1312C>T | 3     |
| L11285 | L11285 | 601263 | GEN-1K7 | GEN-1K7 | Homosapiens ERK activator kinase (MEK2) mRNA                                         | 1457 | 1458C>A | 3     |
| L11285 | L11285 | 601263 | GEN-1K7 | GEN-1K7 | Homosapiens ERK activator kinase (MEK2) mRNA                                         | 1459 | 1460A>C | 3     |
| L11667 | L11667 | 601753 | GEN-H   | GEN-H   | Cyclophilin D 40kDa mRNA                                                             | 1003 | 904C>A  | L302I |
| L11667 | L11667 | 601753 | GEN-H   | GEN-H   | Cyclophilin D 40kDa                                                                  | 1283 | 1184A>G | 3     |
| L11667 | L11667 | 601753 | GEN-H   | GEN-H   | Cyclophilin D 40kDa                                                                  | 1479 | 1380T>A | 3     |
| L11667 | L11667 | 601753 | GEN-H   | GEN-H   | Cyclophilin D 40kDa                                                                  | 1519 | 1420T>C | 3     |
| L11931 | L11931 | 182144 | GEN-4DT | GEN-4DT | Human cytosolic serine hydroxymethyltransferase (SHMT) mRNA, complete cds            | 1444 | 1420C>T | L474F |
| L11931 | L11931 | 182144 | GEN-4DT | GEN-4DT | Human cytosolic serine hydroxymethyltransferase (SHMT) mRNA, complete cds            | 1541 | 1517C>T | 3     |
| L12052 | L12052 | 171885 | GEN-1LK | GEN-1LK | Human cAMP phosphodiesterase mRNA, 3 end                                             | 1707 | 1707G>A | 3     |
| L12691 | L12691 | 125220 | GEN-ST  | GEN-ST  | Human neutrophil peptide-3 gene, complete cds                                        | 244  | 194A>C  | D65A  |
| L12691 | L12691 | 125220 | GEN-ST  | GEN-ST  | Human neutrophil peptide-3 gene, complete cds                                        | 433  | 383T>C  | 3     |
| MDCR   | L13385 | 601545 | GEN-106 | GEN-106 | Homo sapiens(clone 71) Miller-Dieker lissencephaly protein (LIS1) mRNA, complete cds | 1467 | 1250C>T | 3     |
| MDCR   | L13385 | 601545 | GEN-106 | GEN-106 | Homo sapiens(clone 71) Miller-Dieker lissencephaly protein (LIS1) mRNA, complete cds | 1868 | 1651C>T | 3     |

|        |        |        |         |                                                                                      |      |         |       |
|--------|--------|--------|---------|--------------------------------------------------------------------------------------|------|---------|-------|
| MDCR   | L13385 | 601545 | GEN-106 | Homo sapiens(clone 71) Miller-Dieker lissencephaly protein (LIS1) mRNA, complete cds | 1917 | 1700C>T | 3     |
| MDCR   | L13385 | 601545 | GEN-106 | Homo sapiens(clone 71) Miller-Dieker lissencephaly protein (LIS1) mRNA, complete cds | 2962 | 2745G>T | 3     |
| MDCR   | L13385 | 601545 | GEN-106 | Homo sapiens(clone 71) Miller-Dieker lissencephaly protein (LIS1) mRNA, complete cds | 4589 | 4372G>A | 3     |
| L14754 | L14754 | 600502 | GEN-D9  | DNA-binding protein (SMBP2)                                                          | 2129 | 2080C>T | R694W |
| L14754 | L14754 | 600502 | GEN-D9  | DNA-binding protein (SMBP2)                                                          | 2365 | 2316C>T | S     |
| L14754 | L14754 | 600502 | GEN-D9  | DNA-binding protein (SMBP2)                                                          | 3696 | 3647C>T | 3     |
| L14754 | L14754 | 600502 | GEN-D9  | DNA-binding protein (SMBP2)                                                          | 3712 | 3663T>C | 3     |
| L14754 | L14754 | 600502 | GEN-D9  | DNA-binding protein (SMBP2)                                                          | 3771 | 3722C>G | 3     |
| BF     | L15702 | 138470 | GEN-1UA | Human complement factor B mRNA, complete cds                                         | 135  | 95A>G   | Q32R  |
| L19067 | L19067 | 164014 | GEN-DE  | TRANSCRIPTION FACTOR P65                                                             | 1129 | 1091C>T | S364L |
| L19956 | L19956 | 600641 | GEN-LVE | Human aryl sulfotransferase mRNA, complete cds                                       | 243  | 105A>G  | S     |
| L19956 | L19956 | 600641 | GEN-LVE | Human aryl sulfotransferase mRNA, complete cds                                       | 284  | 146C>T  | S49F  |
| L20298 | L20298 | 121360 | GEN-DH  | Transcription Factor (CBFB)                                                          | 2696 | 2696A>G | 3     |
| L20463 | L20463 | 600445 | GEN-M   | G-protein coupled adenosine A3 receptor                                              | 1671 | 1380A>G | 3     |
| L22214 | L22214 | 102775 | GEN-2S  | Adenosine A1 receptor (ADORA1)                                                       | 557  | 147G>C  | S     |
| L22214 | L22214 | 102775 | GEN-2S  | Adenosine A1 receptor (ADORA1)                                                       | 2622 | 2212G>A | 3     |
| L22473 | L22473 | 600040 | GEN-    | Human Bax alpha mRNA,                                                                | 552  | 552G>A  | S     |

|        |        |        |                |                                                            |      |           |       |
|--------|--------|--------|----------------|------------------------------------------------------------|------|-----------|-------|
| SLC6A3 | L24178 | 126455 | L9D<br>GEN-283 | complete cds<br>Homo sapiens dopamine<br>transporter mRNA, | 1917 | 1898C>T   | 3     |
| L24470 | L24470 | 600563 | GEN-O          | complete cds<br>PROSTAGLANDIN F<br>RECEPTOR                | 1422 | 1185T>C   | 3     |
| L24470 | L24470 | 600563 | GEN-O          | PROSTAGLANDIN F<br>RECEPTOR                                | 1490 | 1253C>T   | 3     |
| L24470 | L24470 | 600563 | GEN-O          | PROSTAGLANDIN F<br>RECEPTOR                                | 1517 | 1280A>G   | 3     |
| L24470 | L24470 | 600563 | GEN-O          | PROSTAGLANDIN F<br>RECEPTOR                                | 2244 | 2007A>G   | 3     |
| L24470 | L24470 | 600563 | GEN-O          | PROSTAGLANDIN F<br>RECEPTOR                                | 2299 | 2062A>G   | 3     |
| OPRM1  | L25119 | 600018 | GEN-<br>4EP    | Human Mu opiate receptor<br>(MOR1) mRNA, complete<br>cds   | 41   | (-172)G>T | 5     |
| OPRM1  | L25119 | 600018 | GEN-<br>4EP    | Human Mu opiate receptor<br>(MOR1) mRNA, complete<br>cds   | 102  | (-111)C>T | 5     |
| OPRM1  | L25119 | 600018 | GEN-<br>4EP    | Human Mu opiate receptor<br>(MOR1) mRNA, complete<br>cds   | 229  | 17C>T     | A6V   |
| OPRM1  | L25119 | 600018 | GEN-<br>4EP    | Human Mu opiate receptor<br>(MOR1) mRNA, complete<br>cds   | 229  | 17C>T     | A6V   |
| OPRM1  | L25119 | 600018 | GEN-<br>4EP    | Human Mu opiate receptor<br>(MOR1) mRNA, complete<br>cds   | 236  | 24G>A     | S     |
| OPRM1  | L25119 | 600018 | GEN-<br>4EP    | Human Mu opiate receptor<br>(MOR1) mRNA, complete<br>cds   | 330  | 118A>G    | N40D  |
| OPRM1  | L25119 | 600018 | GEN-<br>4EP    | Human Mu opiate receptor<br>(MOR1) mRNA, complete<br>cds   | 330  | 118A>G    | N40D  |
| OPRM1  | L25119 | 600018 | GEN-<br>4EP    | Human Mu opiate receptor<br>(MOR1) mRNA, complete<br>cds   | 991  | 779G>A    | R260H |
| OPRM1  | L25119 | 600018 | GEN-<br>4EP    | Human Mu opiate receptor<br>(MOR1) mRNA, complete<br>cds   | 1005 | 793C>T    | R265C |

|        |        |        |         |                                                                    |      |         |        |
|--------|--------|--------|---------|--------------------------------------------------------------------|------|---------|--------|
| OPRM1  | L25119 | 600018 | GEN-4EP | Human Mu opiate receptor (MOR1) mRNA, complete cds                 | 1154 | 942G>A  | S      |
| OPRM1  | L25119 | 600018 | GEN-4EP | Human Mu opiate receptor (MOR1) mRNA, complete cds                 | 1154 | 942G>A  | S      |
| L25259 | L25259 | 601020 | GEN-298 | Human CTLA4 counter-receptor (B7-2) mRNA, complete cds             | 1034 | 928G>A  | A310T  |
| PTGER2 | L28175 | 601586 | GEN-7C  | Prostaglandin E receptor 2 (subtype EP2), 53kD                     | 547  | 159C>T  | S      |
| PTGER2 | L28175 | 601586 | GEN-7C  | Prostaglandin E receptor 2 (subtype EP2), 53kD                     | 611  | 223G>A  | V75M   |
| PTGER2 | L28175 | 601586 | GEN-7C  | Prostaglandin E receptor 2 (subtype EP2), 53kD                     | 1725 | 1337A>G | Q446R  |
| L31584 | L31584 | 600242 | GEN-MDW | Human G protein-coupled receptor (EBI 1) gene                      | 608  | 545T>G  | I182S  |
| L31773 | L31773 | 104220 | GEN-4DD | Adrenergic receptor alpha 1b                                       | 171  | 171C>T  | S      |
| L31773 | L31773 | 104220 | GEN-4DD | Adrenergic receptor alpha 1b                                       | 534  | 534C>T  | S      |
| L31773 | L31773 | 104220 | GEN-4DD | Adrenergic receptor alpha 1b                                       | 549  | 549G>A  | S      |
| NRAMP1 | L32185 | 600266 | GEN-21Y | Homo sapiens integral membrane protein (NRAMP1) mRNA, complete cds | 1399 | 1323C>T | S      |
| L33798 | L33798 | 114208 | GEN-Q   | Ca Channel alpha1s L-Type                                          | 5667 | 5442C>G | S      |
| L33798 | L33798 | 114208 | GEN-Q   | Ca Channel alpha1s L-Type                                          | 5669 | 5444G>C | G1815A |
| L33798 | L33798 | 114208 | GEN-Q   | Ca Channel alpha1s L-Type                                          | 5745 | 5520C>G | D1840E |
| L33798 | L33798 | 114208 | GEN-Q   | Ca Channel alpha1s L-Type                                          | 5941 | 5716C>A | 3      |
| L33798 | L33798 | 114208 | GEN-Q   | Ca Channel alpha1s L-Type                                          | 5971 | 5746C>A | 3      |
| L33798 | L33798 | 114208 | GEN-Q   | Ca Channel alpha1s L-Type                                          | 5985 | 5760G>A | 3      |
| L36719 | L36719 | 602315 | GEN-2NE | Homo sapiens MAP kinase 3 (MKK3) mRNA,                             | 1227 | 890C>A  | T297N  |

|        |        |        |         |                                                                                                             |      |                |       |
|--------|--------|--------|---------|-------------------------------------------------------------------------------------------------------------|------|----------------|-------|
| L36719 | L36719 | 602315 | GEN-2NE | Homo sapiens MAP kinase kinase 3 (MKK3) mRNA, complete cds                                                  | 1271 | 934A>G         | K312E |
| NRAMP2 | L37347 | 600523 | GEN-206 | Human integral membrane protein (Nramp2) mRNA, partial cds                                                  | 1092 | 1083C>T        | S     |
| ALCAM  | L38608 | 601662 | GEN-2PJ | Homo sapiens CD6 ligand (ALCAM) mRNA, complete cds                                                          | 1401 | 1338G>A        | S     |
| L38928 | L38928 | None   | GEN-2PT | Homo sapiens 5,10-methylenetetrahydrofolate synthetase mRNA, complete cds                                   | 617  | 604A>G         | T202A |
| L40992 | L40992 | 600211 | GEN-2SO | Homo sapiens (clone PEBP2aA1) core-binding factor, runt domain, alpha subunit 1 (CBFA1) mRNA, 3' end of cds | 265  | 265G>A         | V89I  |
| L76191 | L76191 | 601108 | GEN-3OQ | Homo sapiens interleukin-1 receptor-associated kinase (IRAK) mRNA, complete cds                             | 902  | 823G>T         | A275S |
| L76191 | L76191 | 601108 | GEN-3OQ | Homo sapiens interleukin-1 receptor-associated kinase (IRAK) mRNA, complete cds                             | 1051 | 972G>A         | S     |
| L76191 | L76191 | 601108 | GEN-3OQ | Homo sapiens interleukin-1 receptor-associated kinase (IRAK) mRNA, complete cds                             | 2191 | 2112C>T        | S     |
| M10901 | M10901 | 138040 | GEN-2W  | Corticosteroid nuclear receptor b                                                                           | 1220 | 1088A>G        | N363S |
| M10901 | M10901 | 138040 | GEN-2W  | Corticosteroid nuclear receptor b                                                                           | 2024 | 1892-1893AG>AG | S     |
| M10901 | M10901 | 138040 | GEN-2W  | Corticosteroid nuclear receptor b                                                                           | 2024 | 1892-1893delAG | F     |
| M10901 | M10901 | 138040 | GEN-2W  | Corticosteroid nuclear receptor b                                                                           | 2054 | 1922A>T        | D641V |
| M10901 | M10901 | 138040 | GEN-2W  | Corticosteroid nuclear receptor b                                                                           | 2372 | 2240T>G        | I747S |

|        |        |        |         |                                                                 |      |         |        |
|--------|--------|--------|---------|-----------------------------------------------------------------|------|---------|--------|
| M10901 | M10901 | 138040 | GEN-2W  | Corticosteroid nuclear receptor b                               | 2391 | 2259A>C | L753F  |
| M10901 | M10901 | 138040 | GEN-2W  | Corticosteroid nuclear receptor b                               | 2391 | 2259A>T | L753F  |
| M11050 | M11050 | 138040 | GEN-7Y  | Glucocorticoid receptor                                         | 2166 | 2034C>T | S      |
| M11050 | M11050 | 138040 | GEN-7Y  | Glucocorticoid receptor                                         | 3353 | 3221T>G | 3      |
| M11050 | M11050 | 138040 | GEN-7Y  | Glucocorticoid receptor                                         | 3398 | 3266T>G | 3      |
| M11313 | M11313 | 103950 | GEN-E7  | alpha-2-macroglobulin                                           | 1573 | 1530T>A | S      |
| M11313 | M11313 | 103950 | GEN-E7  | alpha-2-macroglobulin                                           | 1799 | 1756C>T | F      |
| M11313 | M11313 | 103950 | GEN-E7  | alpha-2-macroglobulin                                           | 3041 | 2998G>A | V1000I |
| M11313 | M11313 | 103950 | GEN-E7  | alpha-2-macroglobulin                                           | 4474 | 4431A>C | 3      |
| M12807 | M12807 | 186940 | GEN-QG  | Human T-cell surface glycoprotein T4 mRNA, complete cds         | 868  | 793C>T  | R265W  |
| M12824 | M12824 | 186910 | GEN-QH  | Human T-cell differentiation antigen Leu-2/T8 mRNA, partial cds | 1545 | 1458C>T | 3      |
| M12824 | M12824 | 186910 | GEN-QH  | Human T-cell differentiation antigen Leu-2/T8 mRNA, partial cds | 1765 | 1678C>T | 3      |
| M12959 | M12959 | 186880 | GEN-S   | CD3 glycoprotein on T lymphocytes                               | 431  | 295T>G  | S99A   |
| M12959 | M12959 | 186880 | GEN-S   | CD3 glycoprotein on T lymphocytes                               | 1060 | 924T>C  | 3      |
| M12959 | M12959 | 186880 | GEN-S   | CD3 glycoprotein on T lymphocytes                               | 1129 | 993C>A  | 3      |
| M12959 | M12959 | 186880 | GEN-S   | CD3 glycoprotein on T lymphocytes                               | 1343 | 1207T>C | 3      |
| M12959 | M12959 | 186880 | GEN-S   | CD3 glycoprotein on T lymphocytes                               | 1345 | 1209G>C | 3      |
| M12959 | M12959 | 186880 | GEN-S   | CD3 glycoprotein on T lymphocytes                               | 1394 | 1258T>G | 3      |
| M12959 | M12959 | 186880 | GEN-S   | CD3 glycoprotein on T lymphocytes                               | 1463 | 1327G>A | 3      |
| C1NH   | M13690 | 106100 | GEN-1P6 | Human plasma protease (C1) inhibitor mRNA, complete cds         | 1475 | 1438G>A | V480M  |
| C1NH   | M13690 | 106100 | GEN-1P6 | Human plasma protease (C1) inhibitor mRNA, complete cds         | 1595 | 1558C>T | 3      |

|        |        |        |         |                                                                                                         |      |            |       |
|--------|--------|--------|---------|---------------------------------------------------------------------------------------------------------|------|------------|-------|
| C1NH   | M13690 | 106100 | GEN-1P6 | Human plasma protease (C1) inhibitor mRNA, complete cds                                                 | 1714 | 1677A>C    | 3     |
| BCL2   | M13994 | 151430 | GEN-1Q9 | Human B-cell leukemia/lymphoma 2 (bcl-2) proto-oncogene mRNA encoding bcl-2-alpha protein, complete cds | 1744 | 286G>A     | A96T  |
| BCL2   | M13994 | 151430 | GEN-1Q9 | Human B-cell leukemia/lymphoma 2 (bcl-2) proto-oncogene mRNA encoding bcl-2-alpha protein, complete cds | 1786 | 328G>C     | G110R |
| BCL2   | M13994 | 151430 | GEN-1Q9 | Human B-cell leukemia/lymphoma 2 (bcl-2) proto-oncogene mRNA encoding bcl-2-alpha protein, complete cds | 2959 | 1501A>G    | 3     |
| C1R    | M14058 | 216950 | GEN-1QJ | Human complement C1r mRNA, complete cds                                                                 | 1519 | 1456C>T    | R486C |
| ARG1   | M14502 | 207800 | GEN-1RE | Human liver arginase mRNA, complete cds                                                                 | 800  | 744C>T     | S     |
| NGFR   | M14764 | 162010 | GEN-1S8 | Human nerve growth factor receptor mRNA, complete cds                                                   | 2716 | 2603C>T    | 3     |
| NGFR   | M14764 | 162010 | GEN-1S8 | Human nerve growth factor receptor mRNA, complete cds                                                   | 2729 | 2616C>T    | 3     |
| NGFR   | M14764 | 162010 | GEN-1S8 | Human nerve growth factor receptor mRNA, complete cds                                                   | 2912 | 2799G>A    | 3     |
| NGFR   | M14764 | 162010 | GEN-1S8 | Human nerve growth factor receptor mRNA, complete cds                                                   | 3252 | 3139C>G    | 3     |
| M14766 | M14766 | 151445 | GEN-QQ  | Human Fc-epsilon receptor CD23 antigen (IgE receptor) mRNA complete cds                                 | 1338 | 1153G>A    | 3     |
| M15169 | M15169 | 109690 | GEN-T   | Beta2 Adrenergic Receptor                                                                               | 466  | (-1122)C>G | 5     |
| M15169 | M15169 | 109690 | GEN-T   | Beta2 Adrenergic Receptor                                                                               | 565  | (-1023)G>A | 5     |
| M15169 | M15169 | 109690 | GEN-T   | Beta2 Adrenergic Receptor                                                                               | 1182 | (-406)C>T  | 5     |



|        |        |        |         |                                                              |      |           |       |
|--------|--------|--------|---------|--------------------------------------------------------------|------|-----------|-------|
| M15169 | M15169 | 109690 | GEN-T   | Beta2 Adrenergic Receptor                                    | 1221 | (-367)C>T | 5     |
| M15169 | M15169 | 109690 | GEN-T   | Beta2 Adrenergic Receptor                                    | 1326 | (-262)G>A | 5     |
| M15169 | M15169 | 109690 | GEN-T   | Beta2 Adrenergic Receptor                                    | 1541 | (-47)C>T  | 5     |
| M15169 | M15169 | 109690 | GEN-T   | Beta2 Adrenergic Receptor                                    | 1633 | 46A>G     | R16G  |
| M15169 | M15169 | 109690 | GEN-T   | Beta2 Adrenergic Receptor                                    | 1633 | 46A>G     | R16G  |
| M15169 | M15169 | 109690 | GEN-T   | Beta2 Adrenergic Receptor                                    | 1666 | 79C>G     | Q27E  |
| M15169 | M15169 | 109690 | GEN-T   | Beta2 Adrenergic Receptor                                    | 1666 | 79C>G     | Q27E  |
| M15169 | M15169 | 109690 | GEN-T   | Beta2 Adrenergic Receptor                                    | 1666 | 79C>G     | Q27E  |
| M15169 | M15169 | 109690 | GEN-T   | Beta2 Adrenergic Receptor                                    | 1687 | 100G>A    | V34M  |
| M15169 | M15169 | 109690 | GEN-T   | Beta2 Adrenergic Receptor                                    | 1839 | 252G>A    | S     |
| M15169 | M15169 | 109690 | GEN-T   | Beta2 Adrenergic Receptor                                    | 2110 | 523C>A    | S     |
| M15169 | M15169 | 109690 | GEN-T   | Beta2 Adrenergic Receptor                                    | 2640 | 1053G>C   | S     |
| M15169 | M15169 | 109690 | GEN-T   | Beta2 Adrenergic Receptor                                    | 2826 | 1239G>A   | S     |
| M15169 | M15169 | 109690 | GEN-T   | Beta2 Adrenergic Receptor                                    | 2862 | 1275C>G   | 3     |
| M15169 | M15169 | 109690 | GEN-T   | Beta2 Adrenergic Receptor                                    | 2864 | 1277C>A   | 3     |
| M15169 | M15169 | 109690 | GEN-T   | Beta2 Adrenergic Receptor                                    | 2865 | 1278C>A   | 3     |
| M15169 | M15169 | 109690 | GEN-T   | Beta2 Adrenergic Receptor                                    | 3371 | 1784A>T   | 3     |
| M15395 | M15395 | 600065 | GEN-U   | Leukocyte integrin beta-2                                    | 890  | 818G>A    | G273E |
| M15395 | M15395 | 600065 | GEN-U   | Leukocyte integrin beta-2                                    | 978  | 906A>G    | S     |
| M15395 | M15395 | 600065 | GEN-U   | Leukocyte integrin beta-2                                    | 1173 | 1101C>A   | S     |
| M15395 | M15395 | 600065 | GEN-U   | Leukocyte integrin beta-2                                    | 1395 | 1323T>C   | S     |
| M15395 | M15395 | 600065 | GEN-U   | Leukocyte integrin beta-2                                    | 1614 | 1542C>T   | S     |
| M15395 | M15395 | 600065 | GEN-U   | Leukocyte integrin beta-2                                    | 1965 | 1893C>T   | S     |
| M15395 | M15395 | 600065 | GEN-U   | Leukocyte integrin beta-2                                    | 2505 | 2433G>A   | 3     |
| M15395 | M15395 | 600065 | GEN-U   | Leukocyte integrin beta-2                                    | 2505 | 2433G>A   | 3     |
| M15395 | M15395 | 600065 | GEN-U   | Leukocyte integrin beta-2                                    | 2528 | 2456C>A   | 3     |
| M15395 | M15395 | 600065 | GEN-U   | Leukocyte integrin beta-2                                    | 2528 | 2456C>A   | 3     |
| M15395 | M15395 | 600065 | GEN-U   | Leukocyte integrin beta-2                                    | 2553 | 2481G>C   | 3     |
| M15395 | M15395 | 600065 | GEN-U   | Leukocyte integrin beta-2                                    | 1160 | 1160A>C   | 3     |
| DAF    | M15799 | 125240 | GEN-1UD | Human complement decay-accelerating factor (DAF) mRNA; 3 end |      |           |       |
| M16405 | M16405 | None   | GEN-4ES | Muscarinic receptor, CHRM4                                   | 2138 | 1338C>T   | S     |
| M16405 | M16405 | None   | GEN-4ES | Muscarinic receptor, CHRM4                                   | 2409 | 1609G>A   | 3     |
| M16541 | M16541 | 177400 | GEN-35  | Butyrylcholinesterase                                        | 422  | 293A>G    | D98G  |

|        |        |        |         |                                                             |      |                    |       |
|--------|--------|--------|---------|-------------------------------------------------------------|------|--------------------|-------|
| M16541 | M16541 | 177400 | GEN-35  | Butyrylcholinesterase                                       | 557  | 428G>A             | G143D |
| M16541 | M16541 | 177400 | GEN-35  | Butyrylcholinesterase                                       | 564  | 435-<br>436TT>AG>A | F146V |
| M16541 | M16541 | 177400 | GEN-35  | Butyrylcholinesterase                                       | 568  | G<br>439C>T        | F     |
| M16541 | M16541 | 177400 | GEN-35  | Butyrylcholinesterase                                       | 596  | 467A>G             | Y156C |
| M16541 | M16541 | 177400 | GEN-35  | Butyrylcholinesterase                                       | 941  | 812C>T             | T271M |
| M16541 | M16541 | 177400 | GEN-35  | Butyrylcholinesterase                                       | 961  | 832A>C             | T278P |
| M16541 | M16541 | 177400 | GEN-35  | Butyrylcholinesterase                                       | 978  | 849G>C             | E283D |
| M16541 | M16541 | 177400 | GEN-35  | Butyrylcholinesterase                                       | 1201 | 1072T>A            | L358I |
| M16541 | M16541 | 177400 | GEN-35  | Butyrylcholinesterase                                       | 1306 | 1177G>A            | G393R |
| M16541 | M16541 | 177400 | GEN-35  | Butyrylcholinesterase                                       | 1382 | 1253G>T            | G418V |
| M16541 | M16541 | 177400 | GEN-35  | Butyrylcholinesterase                                       | 1549 | 1420T>G            | F474V |
| M16541 | M16541 | 177400 | GEN-35  | Butyrylcholinesterase                                       | 1564 | 1435G>T            | F     |
| M16541 | M16541 | 177400 | GEN-35  | Butyrylcholinesterase                                       | 1703 | 1574A>T            | E525V |
| M16541 | M16541 | 177400 | GEN-35  | Butyrylcholinesterase                                       | 1756 | 1627C>T            | R543C |
| M16541 | M16541 | 177400 | GEN-35  | Butyrylcholinesterase                                       | 1828 | 1699G>A            | A567T |
| M16541 | M16541 | 177400 | GEN-35  | Butyrylcholinesterase                                       | 1828 | 1699G>A            | A567T |
| M16541 | M16541 | 177400 | GEN-35  | Butyrylcholinesterase                                       | 2127 | 1998A>G            | 3     |
| M16541 | M16541 | 177400 | GEN-35  | Butyrylcholinesterase                                       | 2127 | 1998A>G            | 3     |
| M16541 | M16973 | 120960 | GEN-1ZA | Human complement protein C8 beta subunit mRNA, complete cds | 1860 | 1833C>T            | 3     |
| CYP21  | M17252 | 201910 | GEN-201 | Human cytochrome P450c21 mRNA, 3 end                        | 224  | 224G>A             | R75H  |
| CYP21  | M17252 | 201910 | GEN-201 | Human cytochrome P450c21 mRNA, 3 end                        | 330  | 330C>T             | S     |
| CYP21  | M17252 | 201910 | GEN-201 | Human cytochrome P450c21 mRNA, 3 end                        | 745  | 745T>C             | 3     |
| C8G    | M17999 | 120930 | GEN-20Y | Human complement component C8-gamma mRNA, complete cds      | 193  | 132T>G             | S     |
| M19045 | M19045 | 153450 | GEN-QZ  | Human lysozyme mRNA, complete cds                           | 156  | 143G>T             | C48F  |
| M19045 | M19045 | 153450 | GEN-QZ  | Human lysozyme mRNA, complete cds                           | 638  | 625T>C             | 3     |
| M19045 | M19045 | 153450 | GEN-QZ  | Human lysozyme mRNA, complete cds                           | 825  | 812A>G             | 3     |

|        |        |        |             |                                                                         |      |         |       |
|--------|--------|--------|-------------|-------------------------------------------------------------------------|------|---------|-------|
| M19045 | M19045 | 153450 | GEN-QZ      | Human lysozyme mRNA,<br>complete cds                                    | 876  | 863T>C  | 3     |
| M19045 | M19045 | 153450 | GEN-QZ      | Human lysozyme mRNA,<br>complete cds                                    | 939  | 926C>T  | 3     |
| M19045 | M19045 | 153450 | GEN-QZ      | Human lysozyme mRNA,<br>complete cds                                    | 973  | 960T>C  | 3     |
| M19045 | M19045 | 153450 | GEN-QZ      | Human lysozyme mRNA,<br>complete cds                                    | 981  | 968A>G  | 3     |
| M19045 | M19045 | 153450 | GEN-QZ      | Human lysozyme mRNA,<br>complete cds                                    | 1018 | 1005G>A | 3     |
| M19045 | M19045 | 153450 | GEN-QZ      | Human lysozyme mRNA,<br>complete cds                                    | 1304 | 1291C>T | 3     |
| M20137 | M20137 | 147740 | GEN-<br>CCJ | Human interleukin 3 (IL-3)<br>mRNA, complete cds,<br>clone pcD-SR-alpha | 132  | 79C>T   | P27S  |
| M20566 | M20566 | 147880 | GEN-3A      | Interleukin 6A                                                          | 3058 | 2621A>T | 3     |
| M21054 | M21054 | 172410 | GEN-3B      | Phospholipase A-2 (PLA-2)<br>lung                                       | 331  | 294G>A  | S     |
| M21054 | M21054 | 172410 | GEN-3B      | Phospholipase A-2 (PLA-2)<br>lung                                       | 400  | 363C>A  | D121E |
| SCYA5  | M21121 | 187011 | GEN-<br>24E | Human T cell-specific<br>protein (RANTES) mRNA,<br>complete cds         | 234  | 208C>T  | R70C  |
| SCYA5  | M21121 | 187011 | GEN-<br>24E | Human T cell-specific<br>protein (RANTES) mRNA,<br>complete cds         | 524  | 498T>C  | 3     |
| SCYA5  | M21121 | 187011 | GEN-<br>24E | Human T cell-specific<br>protein (RANTES) mRNA,<br>complete cds         | 634  | 608C>T  | 3     |
| SCYA5  | M21121 | 187011 | GEN-<br>24E | Human T cell-specific<br>protein (RANTES) mRNA,<br>complete cds         | 666  | 640C>T  | 3     |
| SCYA5  | M21121 | 187011 | GEN-<br>24E | Human T cell-specific<br>protein (RANTES) mRNA,<br>complete cds         | 667  | 641G>A  | 3     |
| SCYA5  | M21121 | 187011 | GEN-<br>24E | Human T cell-specific<br>protein (RANTES) mRNA,<br>complete cds         | 690  | 664G>A  | 3     |
| SCYA5  | M21121 | 187011 | GEN-<br>24E | Human T cell-specific<br>protein (RANTES) mRNA,<br>complete cds         | 695  | 669C>T  | 3     |

|        |        |        |         |                                                                          |      |         |       |
|--------|--------|--------|---------|--------------------------------------------------------------------------|------|---------|-------|
| SCYA5  | M21121 | 187011 | GEN-24E | Human T cell-specific protein (RANTES) mRNA, complete cds                | 696  | 670G>A  | 3     |
| SCYA5  | M21121 | 187011 | GEN-24E | Human T cell-specific protein (RANTES) mRNA, complete cds                | 698  | 672G>A  | 3     |
| SCYA5  | M21121 | 187011 | GEN-24E | Human T cell-specific protein (RANTES) mRNA, complete cds                | 702  | 676C>A  | 3     |
| SCYA5  | M21121 | 187011 | GEN-24E | Human T cell-specific protein (RANTES) mRNA, complete cds                | 719  | 693C>T  | 3     |
| SCYA5  | M21121 | 187011 | GEN-24E | Human T cell-specific protein (RANTES) mRNA, complete cds                | 728  | 702G>A  | 3     |
| SCYA5  | M21121 | 187011 | GEN-24E | Human T cell-specific protein (RANTES) mRNA, complete cds                | 735  | 709C>T  | 3     |
| SCYA5  | M21121 | 187011 | GEN-24E | Human T cell-specific protein (RANTES) mRNA, complete cds                | 736  | 710G>A  | 3     |
| M22324 | M22324 | 151530 | GEN-25R | Human aminopeptidase N/CD13 mRNA encoding aminopeptidase N, complete cds | 1052 | 932C>T  | A311V |
| M22324 | M22324 | 151530 | GEN-25R | Human aminopeptidase N/CD13 mRNA encoding aminopeptidase N, complete cds | 2168 | 2048C>G | T683S |
| M22324 | M22324 | 151530 | GEN-25R | Human aminopeptidase N/CD13 mRNA encoding aminopeptidase N, complete cds | 2375 | 2255G>A | S752N |
| M22324 | M22324 | 151530 | GEN-25R | Human aminopeptidase N/CD13 mRNA encoding aminopeptidase N, complete cds | 2505 | 2385C>T | S     |
| M22324 | M22324 | 151530 | GEN-25R | Human aminopeptidase N/CD13 mRNA encoding aminopeptidase N, complete cds | 3053 | 2933G>C | 3     |

|         |        |        |         |                                                                          |      |              |       |
|---------|--------|--------|---------|--------------------------------------------------------------------------|------|--------------|-------|
| M22324  | M22324 | 15130  | GEN-25R | Human aminopeptidase N/CD13 mRNA encoding aminopeptidase N, complete cds | 3299 | 3179A>G      | 3     |
| M22324  | M22324 | 15130  | GEN-25R | Human aminopeptidase N/CD13 mRNA encoding aminopeptidase N, complete cds | 3405 | 3285C>T      | 3     |
| PLA2G2A | M22430 | 172411 | GEN-25V | Human RASf-A PLA2 mRNA, complete cds                                     | 116  | (-20)G>T     | 5     |
| PLA2G2A | M22430 | 172411 | GEN-25V | Human RASf-A PLA2 mRNA, complete cds                                     | 231  | 96G>C        | S     |
| PLA2G2A | M22430 | 172411 | GEN-25V | Human RASf-A PLA2 mRNA, complete cds                                     | 267  | 132C>T       | S     |
| PLA2G2A | M22430 | 172411 | GEN-25V | Human RASf-A PLA2 mRNA, complete cds                                     | 267  | 132C>T       | S     |
| PLA2G2A | M22430 | 172411 | GEN-25V | Human RASf-A PLA2 mRNA, complete cds                                     | 278  | 143-144GT>GT | S     |
| PLA2G2A | M22430 | 172411 | GEN-25V | Human RASf-A PLA2 mRNA, complete cds                                     | 278  | 143-144delGT | F     |
| PLA2G2A | M22430 | 172411 | GEN-25V | Human RASf-A PLA2 mRNA, complete cds                                     | 643  | 508C>T       | 3     |
| PLA2G2A | M22430 | 172411 | GEN-25V | Human RASf-A PLA2 mRNA, complete cds                                     | 700  | 565G>C       | 3     |
| M24283  | M24283 | 147840 | GEN-V   | Intercellular adhesion molecule 1                                        | 238  | 167A>T       | K56M  |
| M24283  | M24283 | 147840 | GEN-V   | Intercellular adhesion molecule 1                                        | 238  | 167A>T       | K56M  |
| M24283  | M24283 | 147840 | GEN-V   | Intercellular adhesion molecule 1                                        | 792  | 721G>A       | G241R |
| M24283  | M24283 | 147840 | GEN-V   | Intercellular adhesion molecule 1                                        | 792  | 721G>A       | G241R |
| M24283  | M24283 | 147840 | GEN-V   | Intercellular adhesion molecule 1                                        | 1126 | 1055C>T      | P352L |
| M24283  | M24283 | 147840 | GEN-V   | Intercellular adhesion molecule 1                                        | 1166 | 1095C>T      | S     |
| M24283  | M24283 | 147840 | GEN-V   | Intercellular adhesion molecule 1                                        | 1295 | 1224G>A      | S     |
| M24283  | M24283 | 147840 | GEN-V   | Intercellular adhesion molecule 1                                        | 1476 | 1405A>G      | K469E |
| M24283  | M24283 | 147840 | GEN-V   | Intercellular adhesion molecule 1                                        | 1476 | 1405A>G      | K469E |

|        |        |        |         |                                                     |      |           |       |
|--------|--------|--------|---------|-----------------------------------------------------|------|-----------|-------|
| M24283 | M24283 | 147840 | GEN-V   | molecule 1                                          | 1476 | 1405A>G   | K469E |
|        |        |        |         | Intercellular adhesion molecule 1                   |      |           |       |
| M24283 | M24283 | 147840 | GEN-V   | Intercellular adhesion molecule 1                   | 2043 | 1972C>T   | 3     |
| M24283 | M24283 | 147840 | GEN-V   | Intercellular adhesion molecule 1                   | 2043 | 1972C>T   | 3     |
| M24283 | M24283 | 147840 | GEN-V   | Intercellular adhesion molecule 1                   | 2551 | 2480C>T   | 3     |
| M24283 | M24283 | 147840 | GEN-V   | Intercellular adhesion molecule 1                   | 2681 | 2610G>A   | 3     |
| M24283 | M24283 | 147840 | GEN-V   | Intercellular adhesion molecule 1                   | 2842 | 2771G>A   | 3     |
| M24283 | M24283 | 147840 | GEN-V   | Intercellular adhesion molecule 1                   | 2842 | 2771G>A   | 3     |
| M24283 | M24283 | 147840 | GEN-V   | Intercellular adhesion molecule 1                   | 2935 | 2864T>C   | 3     |
| M24283 | M24283 | 147840 | GEN-V   | Intercellular adhesion molecule 1                   | 2938 | 2867G>A   | 3     |
| M24283 | M24283 | 147840 | GEN-V   | Intercellular adhesion molecule 1                   | 2950 | 2879C>T   | 3     |
| CD36   | M24795 | 173510 | GEN-28R | Human CD36 antigen mRNA, complete cds               | 79   | (-132)C>A | 5     |
| CD36   | M24795 | 173510 | GEN-28R | Human CD36 antigen mRNA, complete cds               | 341  | 131T>G    | L44R  |
| CD36   | M24795 | 173510 | GEN-28R | Human CD36 antigen mRNA, complete cds               | 1851 | 1641A>G   | 3     |
| M24857 | M24857 | 180190 | GEN-80  | Retinoic acid receptor, gamma 1                     | 1694 | 1280C>T   | S427L |
| SELL   | M25280 | 153240 | GEN-29J | Human lymph node homing receptor mRNA, complete cds | 436  | 321T>C    | S     |
| SELL   | M25280 | 153240 | GEN-29J | Human lymph node homing receptor mRNA, complete cds | 692  | 577C>T    | L193F |
| SELL   | M25280 | 153240 | GEN-29J | Human lymph node homing receptor mRNA, complete cds | 1378 | 1263C>T   | 3     |
| SELL   | M25280 | 153240 | GEN-29J | Human lymph node homing receptor mRNA, complete cds | 2157 | 2042A>C   | 3     |

|       |        |        |         |                                                                                        |      |          |      |
|-------|--------|--------|---------|----------------------------------------------------------------------------------------|------|----------|------|
| SELL  | M25280 | 153240 | GEN-29J | Human lymph node,<br>homologous receptor mRNA,<br>complete cds                         | 2215 | 2100C>G  | 3    |
| SCYA3 | M25315 | 601395 | GEN-29M | Homo sapiens (clone pAT<br>464) potential<br>lymphokine/cytokine<br>mRNA, complete cds | 32   | (-52)T>C | 5    |
| SCYA3 | M25315 | 601395 | GEN-29M | Homo sapiens (clone pAT<br>464) potential<br>lymphokine/cytokine<br>mRNA, complete cds | 67   | (-17)G>A | 5    |
| SCYA3 | M25315 | 601395 | GEN-29M | Homo sapiens (clone pAT<br>464) potential<br>lymphokine/cytokine<br>mRNA, complete cds | 110  | 27T>C    | S    |
| SCYA3 | M25315 | 601395 | GEN-29M | Homo sapiens (clone pAT<br>464) potential<br>lymphokine/cytokine<br>mRNA, complete cds | 153  | 70T>C    | S24P |
| SCYA3 | M25315 | 601395 | GEN-29M | Homo sapiens (clone pAT<br>464) potential<br>lymphokine/cytokine<br>mRNA, complete cds | 203  | 120G>A   | S    |
| SCYA3 | M25315 | 601395 | GEN-29M | Homo sapiens (clone pAT<br>464) potential<br>lymphokine/cytokine<br>mRNA, complete cds | 263  | 180C>T   | S    |
| SCYA3 | M25315 | 601395 | GEN-29M | Homo sapiens (clone pAT<br>464) potential<br>lymphokine/cytokine<br>mRNA, complete cds | 264  | 181G>A   | G61S |
| SCYA3 | M25315 | 601395 | GEN-29M | Homo sapiens (clone pAT<br>464) potential<br>lymphokine/cytokine<br>mRNA, complete cds | 285  | 202C>A   | S    |
| SCYA3 | M25315 | 601395 | GEN-29M | Homo sapiens (clone pAT<br>464) potential<br>lymphokine/cytokine<br>mRNA, complete cds | 288  | 205A>G   | S69G |
| SCYA3 | M25315 | 601395 | GEN-29M | Homo sapiens (clone pAT<br>464) potential<br>lymphokine/cytokine<br>mRNA, complete cds | 291  | 208C>G   | R70G |

|        |        |        |             |                                                                                                                       |      |         |       |
|--------|--------|--------|-------------|-----------------------------------------------------------------------------------------------------------------------|------|---------|-------|
| SCYA3  | M25315 | 601395 | GEN-<br>29M | lymphokine/cytokine<br>mRNA, complete cds<br>Homo sapiens (clone pAT<br>464) potential                                | 335  | 252T>C  | S     |
| SCYA3  | M25315 | 601395 | GEN-<br>29M | lymphokine/cytokine<br>mRNA, complete cds<br>Homo sapiens (clone pAT<br>464) potential                                | 341  | 258C>T  | S     |
| SCYA3  | M25315 | 601395 | GEN-<br>29M | lymphokine/cytokine<br>mRNA, complete cds<br>Homo sapiens (clone pAT<br>464) potential                                | 395  | 312G>A  | 3     |
| SCYA3  | M25315 | 601395 | GEN-<br>29M | lymphokine/cytokine<br>mRNA, complete cds<br>Homo sapiens (clone pAT<br>464) potential                                | 452  | 369C>T  | 3     |
| SCYA3  | M25315 | 601395 | GEN-<br>29M | lymphokine/cytokine<br>mRNA, complete cds<br>Homo sapiens (clone pAT<br>464) potential                                | 479  | 396G>A  | 3     |
| SCYA3  | M25315 | 601395 | GEN-<br>29M | lymphokine/cytokine<br>mRNA, complete cds<br>Homo sapiens (clone pAT<br>464) potential                                | 549  | 466G>A  | 3     |
| SCYA3  | M25315 | 601395 | GEN-<br>29M | lymphokine/cytokine<br>mRNA, complete cds<br>Homo sapiens (clone pAT<br>464) potential                                | 561  | 478C>T  | 3     |
| SCYA3  | M25315 | 601395 | GEN-<br>29M | lymphokine/cytokine<br>mRNA, complete cds<br>Homo sapiens (clone pAT<br>464) potential                                | 617  | 534C>G  | 3     |
| SCYA3  | M25315 | 601395 | GEN-<br>29M | lymphokine/cytokine<br>mRNA, complete cds<br>Homo sapiens (clone pAT<br>464) potential                                | 660  | 577A>G  | 3     |
| M25813 | M25813 | None   | GEN-<br>2A0 | lymphokine/cytokine<br>mRNA, complete cds<br>Human unidentified gene<br>complementary to<br>P450c21 gene, partial cds | 1357 | 1357G>A | V453I |



|        |        |        |         |                                                                                            |      |         |       |
|--------|--------|--------|---------|--------------------------------------------------------------------------------------------|------|---------|-------|
| M25813 | M25813 | None   | GEN-2A0 | Human unidentified gene complementary to P450c21 gene, partial cds                         | 2082 | 2082C>G | I694M |
| M25813 | M25813 | None   | GEN-2A0 | Human unidentified gene complementary to P450c21 gene, partial cds                         | 2502 | 2502G>A | 3     |
| M25813 | M25813 | None   | GEN-2A0 | Human unidentified gene complementary to P450c21 gene, partial cds                         | 2626 | 2626A>G | 3     |
| M26383 | M26383 | 146930 | GEN-3E  | Interleukin 8                                                                              | 259  | 185C>G  | A62G  |
| M26383 | M26383 | 146930 | GEN-3E  | Interleukin 8                                                                              | 1237 | 1163A>T | 3     |
| M26383 | M26383 | 146930 | GEN-3E  | Interleukin 8                                                                              | 1281 | 1207A>G | 3     |
| M27492 | M27492 | 147810 | GEN-3F  | INTERLEUKIN 1 RECEPTOR, TYPE I                                                             | 4686 | 4604T>G | 3     |
| M28226 | M28226 | 158105 | GEN-R8  | Human JE gene encoding a monocyte secretory protein mRNA, complete cds                     | 90   | 44C>G   | A15G  |
| M28226 | M28226 | 158105 | GEN-R8  | Human JE gene encoding a monocyte secretory protein mRNA, complete cds                     | 151  | 105C>T  | S     |
| M28226 | M28226 | 158105 | GEN-R8  | Human JE gene encoding a monocyte secretory protein mRNA, complete cds                     | 411  | 365T>C  | 3     |
| POMC   | M28636 | 176830 | GEN-2DG | Adrenocorticotrophic hormone (ACTH)                                                        | 92   | 92C>T   | 3     |
| CFTR   | M28668 | 602421 | GEN-2DF | Human cystic fibrosis mRNA, encoding a presumed transmembrane conductance regulator (CFTR) | 2729 | 2597G>A | C866Y |
| CFTR   | M28668 | 602421 | GEN-2DF | Human cystic fibrosis mRNA, encoding a presumed transmembrane conductance regulator (CFTR) | 5826 | 5694T>C | 3     |
| CD1B   | M28826 | 188360 | GEN-2DO | Human thymocyte antigen CD1b mRNA, complete cds                                            | 886  | 841G>A  | V281M |

|        |        |        |        |                                                                                               |      |           |       |
|--------|--------|--------|--------|-----------------------------------------------------------------------------------------------|------|-----------|-------|
| M29551 | M29551 | 114106 | GEN-F3 | SERINE/THREONINE<br>PROTEIN<br>PHOSPHATASE 2B<br>CATALYTIC SUBUNIT,<br>BETA ISOFORM           | 936  | 820G>A    | V274M |
| M29551 | M29551 | 114106 | GEN-F3 | SERINE/THREONINE<br>PROTEIN<br>PHOSPHATASE 2B<br>CATALYTIC SUBUNIT,<br>BETA ISOFORM           | 2640 | 2524G>A   | 3     |
| M29696 | M29696 | 146661 | GEN-3H | Interleukin 7 receptor                                                                        | 1088 | 1066G>A   | V356I |
| M30640 | M30640 | 131210 | GEN-RB | Human endothelial<br>leukocyte adhesion<br>molecule 1 (ELAM1)<br>mRNA, complete cds           | 3506 | 3366A>G   | 3     |
| M30773 | M30773 | 114106 | GEN-X  | Calcineurin B type I                                                                          | 331  | (-428)T>C | 5     |
| M30773 | M30773 | 114106 | GEN-X  | Calcineurin B type I                                                                          | 1658 | 900C>A    | 3     |
| M30938 | M30938 | 194364 | GEN-F5 | ATP-DEPENDENT DNA<br>HELICASE II, 86 KD<br>SUBUNIT                                            | 1599 | 1572A>G   | S     |
| M30938 | M30938 | 194364 | GEN-F5 | ATP-DEPENDENT DNA<br>HELICASE II, 86 KD<br>SUBUNIT                                            | 2549 | 2522T>C   | 3     |
| M30938 | M30938 | 194364 | GEN-F5 | ATP-DEPENDENT DNA<br>HELICASE II, 86 KD<br>SUBUNIT                                            | 2953 | 2926C>A   | 3     |
| M30938 | M30938 | 194364 | GEN-F5 | ATP-DEPENDENT DNA<br>HELICASE II, 86 KD<br>SUBUNIT                                            | 2953 | 2926C>A   | 3     |
| M30938 | M30938 | 194364 | GEN-F5 | ATP-DEPENDENT DNA<br>HELICASE II, 86 KD<br>SUBUNIT                                            | 3037 | 3010G>A   | 3     |
| M30938 | M30938 | 194364 | GEN-F5 | ATP-DEPENDENT DNA<br>HELICASE II, 86 KD<br>SUBUNIT                                            | 3067 | 3040G>A   | 3     |
| M31523 | M31523 | 147141 | GEN-F7 | Transcription factor 3 (E2A<br>immunoglobulin enhancer<br>binding factors E12/E47)<br>SUBUNIT | 1321 | 1291G>A   | G431S |
| M31523 | M31523 | 147141 | GEN-F7 | Transcription factor 3 (E2A<br>immunoglobulin enhancer<br>binding factors E12/E47)<br>SUBUNIT | 1323 | 1293C>T   | S     |

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|--------|--------|--------|-------------|------------------------------------------------------------------------------------------------------------------|------|---------|-------|
| M31523 | M31523 | 147141 | GEN-F7      | binding factors E12/E47)<br>Transcription factor 3 (E2A<br>immunoglobulin enhancer<br>binding factors E12/E47)   | 1332 | 1302G>A | S     |
| M31523 | M31523 | 147141 | GEN-F7      | Transcription factor 3 (E2A<br>immunoglobulin enhancer<br>binding factors E12/E47)                               | 1338 | 1308T>C | S     |
| M31523 | M31523 | 147141 | GEN-F7      | Transcription factor 3 (E2A<br>immunoglobulin enhancer<br>binding factors E12/E47)                               | 1608 | 1578C>G | S     |
| M31523 | M31523 | 147141 | GEN-F7      | Transcription factor 3 (E2A<br>immunoglobulin enhancer<br>binding factors E12/E47)                               | 4022 | 3992G>A | 3     |
| M31523 | M31523 | 147141 | GEN-F7      | Transcription factor 3 (E2A<br>immunoglobulin enhancer<br>binding factors E12/E47)                               | 4254 | 4224T>A | 3     |
| M32315 | M32315 | 191191 | GEN-3M      | immunoglobulin enhancer<br>binding factors E12/E47)<br>Tumor necrosis factor<br>receptor 2 (75kD)                | 676  | 587T>G  | M196R |
| M32315 | M32315 | 191191 | GEN-3M      | Tumor necrosis factor<br>receptor 2 (75kD)                                                                       | 1176 | 1087G>A | A363T |
| M32315 | M32315 | 191191 | GEN-3M      | Tumor necrosis factor<br>receptor 2 (75kD)                                                                       | 1668 | 1579G>T | 3     |
| M32315 | M32315 | 191191 | GEN-3M      | Tumor necrosis factor<br>receptor 2 (75kD)                                                                       | 2898 | 2809G>A | 3     |
| M32315 | M32315 | 191191 | GEN-3M      | Tumor necrosis factor<br>receptor 2 (75kD)                                                                       | 3671 | 3582G>A | 3     |
| VEGF   | M32977 | 192240 | GEN-2JF     | receptor 2 (75kD)<br>Human heparin-binding<br>vascular endothelial growth<br>factor (VEGF) mRNA,<br>complete cds | 50   | (-7)C>T | 5     |
| VEGF   | M32977 | 192240 | GEN-2JF     | Human heparin-binding<br>vascular endothelial growth<br>factor (VEGF) mRNA,<br>complete cds                      | 92   | 36C>T   | S     |
| M33195 | M33195 | 147139 | GEN-<br>2JR | Human Fc-epsilon-receptor<br>gamma-chain mRNA,<br>complete cds                                                   | 446  | 421T>G  | 3     |
| M33195 | M33195 | 147139 | GEN-<br>2JR | Human Fc-epsilon-receptor<br>gamma-chain mRNA,<br>complete cds                                                   | 489  | 464T>C  | 3     |
| M33491 | M33491 | 191080 | GEN-RD      | Human tryptase-I mRNA, 3                                                                                         | 92   | 92C>T   | S31L  |

|              |        |        |             |                                                                   |      |         |       |
|--------------|--------|--------|-------------|-------------------------------------------------------------------|------|---------|-------|
| M33491       | M33491 | 191080 | GEN-RD      | Human tryptase-I mRNA, 3<br>end                                   | 392  | 392C>G  | T131R |
| M33491       | M33491 | 191080 | GEN-RD      | Human tryptase-I mRNA, 3<br>end                                   | 609  | 609G>A  | S     |
| M33491       | M33491 | 191080 | GEN-RD      | Human tryptase-I mRNA, 3<br>end                                   | 707  | 707G>A  | C236Y |
| M33491       | M33491 | 191080 | GEN-RD      | Human tryptase-I mRNA, 3<br>end                                   | 730  | 730G>A  | A244T |
| M33491       | M33491 | 191080 | GEN-RD      | Human tryptase-I mRNA, 3<br>end                                   | 837  | 837T>G  | 3     |
| M33491       | M33491 | 191080 | GEN-RD      | Human tryptase-I mRNA, 3<br>end                                   | 840  | 840G>T  | 3     |
| M33491       | M33491 | 191080 | GEN-RD      | Human tryptase-I mRNA, 3<br>end                                   | 1008 | 1008T>C | 3     |
| M33491       | M33491 | 191080 | GEN-RD      | Human tryptase-I mRNA, 3<br>end                                   | 1050 | 1050C>T | 3     |
| M33491       | M33491 | 191080 | GEN-RD      | Human tryptase-I mRNA, 3<br>end                                   | 1060 | 1060A>G | 3     |
| M33680       | M33680 | 186845 | GEN-<br>2K3 | Human 26-kDa cell surface<br>protein TAPA-1 mRNA,<br>complete cds | 1065 | 827G>A  | 3     |
| M33680       | M33680 | 186845 | GEN-<br>2K3 | Human 26-kDa cell surface<br>protein TAPA-1 mRNA,<br>complete cds | 1284 | 1046T>C | 3     |
| M33680       | M33680 | 186845 | GEN-<br>2K3 | Human 26-kDa cell surface<br>protein TAPA-1 mRNA,<br>complete cds | 1412 | 1174C>T | 3     |
| M33680       | M33680 | 186845 | GEN-<br>2K3 | Human 26-kDa cell surface<br>protein TAPA-1 mRNA,<br>complete cds | 1416 | 1178G>A | 3     |
| HLA-<br>DQB1 | M33907 | 142857 | GEN-<br>2KB | Human MHC class II HLA-<br>DQB1 mRNA, complete<br>cds             | 561  | 516T>C  | S     |
| HLA-<br>DQB1 | M33907 | 142857 | GEN-<br>2KB | Human MHC class II HLA-<br>DQB1 mRNA, complete<br>cds             | 641  | 596G>A  | R199H |
| HLA-<br>DQB1 | M33907 | 142857 | GEN-<br>2KB | Human MHC class II HLA-<br>DQB1 mRNA, complete<br>cds             | 648  | 603C>T  | S     |
| HLA-<br>DQB1 | M33907 | 142857 | GEN-<br>2KB | Human MHC class II HLA-<br>DQB1 mRNA, complete<br>cds             | 695  | 650T>C  | I217T |

|          |         |                                                                  |      |         |       |
|----------|---------|------------------------------------------------------------------|------|---------|-------|
| DQB1     | 2KB     | DQB1 mRNA, complete<br>cds                                       |      |         |       |
| HLA-DQB1 | GEN-2KB | Human MHC class II HLA-DQB1 mRNA, complete<br>cds                | 771  | 726G>C  | S     |
| HLA-DQB1 | GEN-2KB | Human MHC class II HLA-DQB1 mRNA, complete<br>cds                | 780  | 735C>T  | S     |
| M34539   | GEN-3N  | FKBP, tacrolimus binding protein, FK506-binding protein 1 (12kD) | 449  | 371A>G  | 3     |
| M34539   | GEN-3N  | FKBP, tacrolimus binding protein, FK506-binding protein 1 (12kD) | 486  | 408G>A  | 3     |
| M34539   | GEN-3N  | FKBP, tacrolimus binding protein, FK506-binding protein 1 (12kD) | 650  | 572T>C  | 3     |
| M35011   | GEN-2LV | Human integrin beta-5 subunit mRNA, complete<br>cds              | 1448 | 1419C>T | S     |
| M35011   | GEN-2LV | Human integrin beta-5 subunit mRNA, complete<br>cds              | 2778 | 2749A>C | 3     |
| M35011   | GEN-2LV | Human integrin beta-5 subunit mRNA, complete<br>cds              | 2904 | 2875T>C | 3     |
| M35011   | GEN-2LV | Human integrin beta-5 subunit mRNA, complete<br>cds              | 3077 | 3048G>A | 3     |
| M35011   | GEN-2LV | Human integrin beta-5 subunit mRNA, complete<br>cds              | 3095 | 3066T>A | 3     |
| M35999   | GEN-Y   | Leukocyte integrin beta-3                                        | 53   | 35T>C   | V12A  |
| M35999   | GEN-Y   | Leukocyte integrin beta-3                                        | 149  | 131C>A  | A44D  |
| M35999   | GEN-Y   | Leukocyte integrin beta-3                                        | 194  | 176T>C  | L59P  |
| M35999   | GEN-Y   | Leukocyte integrin beta-3                                        | 364  | 346C>T  | L116F |
| M35999   | GEN-Y   | Leukocyte integrin beta-3                                        | 900  | 882T>C  | S     |
| M35999   | GEN-Y   | Leukocyte integrin beta-3                                        | 987  | 969G>T  | E323D |
| M35999   | GEN-Y   | Leukocyte integrin beta-3                                        | 1161 | 1143C>A | S     |
| M35999   | GEN-Y   | Leukocyte integrin beta-3                                        | 1161 | 1143C>A | S     |

|        |        |        |         |                                                                       |      |         |       |
|--------|--------|--------|---------|-----------------------------------------------------------------------|------|---------|-------|
| M35999 | M35999 | 173470 | GEN-Y   | Leukocyte integrin beta-3                                             | 1551 | 1533G>A | S     |
| M35999 | M35999 | 173470 | GEN-Y   | Leukocyte integrin beta-3                                             | 1551 | 1533G>A | S     |
| M35999 | M35999 | 173470 | GEN-Y   | Leukocyte integrin beta-3                                             | 1562 | 1544G>A | R515Q |
| M35999 | M35999 | 173470 | GEN-Y   | Leukocyte integrin beta-3                                             | 1563 | 1545G>A | S     |
| M35999 | M35999 | 173470 | GEN-Y   | Leukocyte integrin beta-3                                             | 1563 | 1545G>A | S     |
| M35999 | M35999 | 173470 | GEN-Y   | Leukocyte integrin beta-3                                             | 2226 | 2208C>T | S     |
| M35999 | M35999 | 173470 | GEN-Y   | Leukocyte integrin beta-3                                             | 2426 | 2408G>C | 3     |
| M35999 | M35999 | 173470 | GEN-Y   | Leukocyte integrin beta-3                                             | 3056 | 3038C>T | 3     |
| M35999 | M35999 | 173470 | GEN-Y   | Leukocyte integrin beta-3                                             | 3098 | 3080A>G | 3     |
| M35999 | M35999 | 173470 | GEN-Y   | Leukocyte integrin beta-3                                             | 3403 | 3385A>T | 3     |
| M35999 | M35999 | 173470 | GEN-Y   | Leukocyte integrin beta-3                                             | 3927 | 3909C>T | 3     |
| LIG1   | M36067 | 126391 | GEN-2MS | Human DNA ligase I mRNA, complete cds                                 | 2526 | 2406T>C | S     |
| M36712 | M36712 | 186730 | GEN-2NC | Human T lymphocyte surface glycoprotein (CD8-beta) mRNA, complete cds | 1046 | 1001C>A | 3     |
| M36712 | M36712 | 186730 | GEN-2NC | Human T lymphocyte surface glycoprotein (CD8-beta) mRNA, complete cds | 1281 | 1236T>C | 3     |
| M36712 | M36712 | 186730 | GEN-2NC | Human T lymphocyte surface glycoprotein (CD8-beta) mRNA, complete cds | 1326 | 1281C>A | 3     |
| PLCG2  | M37238 | 600220 | GEN-2O1 | Phospholipase C gamma-2                                               | 449  | 297A>G  | S     |
| PLCG2  | M37238 | 600220 | GEN-2O1 | Phospholipase C gamma-2                                               | 883  | 731A>G  | H244R |
| PLCG2  | M37238 | 600220 | GEN-2O1 | Phospholipase C gamma-2                                               | 922  | 770A>T  | H257L |
| PLCG2  | M37238 | 600220 | GEN-2O1 | Phospholipase C gamma-2                                               | 954  | 802C>T  | R268W |
| PLCG2  | M37238 | 600220 | GEN-2O1 | Phospholipase C gamma-2                                               | 1301 | 1149T>C | S     |
| PLCG2  | M37238 | 600220 | GEN-2O1 | Phospholipase C gamma-2                                               | 1649 | 1497T>C | S     |
| PLCG2  | M37238 | 600220 | GEN-2O1 | Phospholipase C gamma-2                                               | 2666 | 2514G>A | S     |
| PLCG2  | M37238 | 600220 | GEN-2O1 | Phospholipase C gamma-2                                               | 3245 | 3093C>T | S     |
| PLCG2  | M37238 | 600220 | GEN-2O1 | Phospholipase C gamma-2                                               | 3245 | 3093C>T | S     |

|         |        |        |     |         |                                                           |      |         |        |
|---------|--------|--------|-----|---------|-----------------------------------------------------------|------|---------|--------|
| PLCG2   | M37238 | 600220 | 201 | GEN-201 | Phospholipase C gamma-2                                   | 3436 | 3284G>A | G1095D |
| PLCG2   | M37238 | 600220 | 201 | GEN-201 | Phospholipase C gamma-2                                   | 4207 | 4055C>G | 3      |
| PECAM1  | M37780 | 173445 | 201 | GEN-201 | Human leukocyte surface protein (CD31) mRNA, complete cds | 152  | 27C>G   | S      |
| PECAM1  | M37780 | 173445 | 201 | GEN-201 | Human leukocyte surface protein (CD31) mRNA, complete cds | 1577 | 1452C>T | S      |
| PECAM1  | M37780 | 173445 | 201 | GEN-201 | Human leukocyte surface protein (CD31) mRNA, complete cds | 1813 | 1688A>G | N563S  |
| PECAM1  | M37780 | 173445 | 201 | GEN-201 | Human leukocyte surface protein (CD31) mRNA, complete cds | 2133 | 2008G>A | G670R  |
| PECAM1  | M37780 | 173445 | 201 | GEN-201 | Human leukocyte surface protein (CD31) mRNA, complete cds | 2400 | 2275G>A | 3      |
| CD9     | M38690 | 143030 | 201 | GEN-201 | Human CD9 antigen mRNA, complete cds                      | 819  | 768T>G  | 3      |
| CD9     | M38690 | 143030 | 201 | GEN-201 | Human CD9 antigen mRNA, complete cds                      | 826  | 775T>G  | 3      |
| CD9     | M38690 | 143030 | 201 | GEN-201 | Human CD9 antigen mRNA, complete cds                      | 947  | 896G>A  | 3      |
| M55040  | M55040 | 100740 | 201 | GEN-201 | acetylcholinesterase                                      | 323  | 167C>T  | P56L   |
| M55040  | M55040 | 100740 | 201 | GEN-201 | acetylcholinesterase                                      | 1154 | 998T>A  | V333E  |
| M55040  | M55040 | 100740 | 201 | GEN-201 | acetylcholinesterase                                      | 1213 | 1057C>A | H353N  |
| M55040  | M55040 | 100740 | 201 | GEN-201 | acetylcholinesterase                                      | 1482 | 1326G>T | S      |
| M55040  | M55040 | 100740 | 201 | GEN-201 | acetylcholinesterase                                      | 1587 | 1431C>T | S      |
| M55040  | M55040 | 100740 | 201 | GEN-201 | acetylcholinesterase                                      | 1587 | 1431C>T | S      |
| M55040  | M55040 | 100740 | 201 | GEN-201 | acetylcholinesterase                                      | 1663 | 1507T>C | F503L  |
| CSNK2A1 | M55265 | 115440 | 201 | GEN-201 | Human casein kinase II alpha subunit mRNA, complete cds   | 193  | 45T>C   | S      |
| CSNK2A1 | M55265 | 115440 | 201 | GEN-201 | Human casein kinase II alpha subunit mRNA, complete cds   | 1007 | 859A>C  | S287R  |
| CSNK2A1 | M55265 | 115440 | 201 | GEN-201 | Human casein kinase II alpha subunit mRNA, complete cds   | 1180 | 1032G>A | S      |

|         |        |        |                |                                                                     |      |         |       |
|---------|--------|--------|----------------|---------------------------------------------------------------------|------|---------|-------|
| CSNK2A1 | M55265 | 115440 | 35Y<br>GEN-35Y | alpha subunit mRNA,<br>complete cds                                 | 1199 | 1051A>G | M351V |
| CSNK2A2 | M55268 | 115442 | GEN-35X        | Human casein kinase II<br>alpha subunit mRNA,<br>complete cds       | 1532 | 1369C>A | 3     |
| M55643  | M55643 | 164011 | GEN-RP         | Human casein kinase II<br>alpha subunit mRNA,<br>complete cds       | 1936 | 1755G>A | S     |
| M57414  | M57414 | None   | GEN-4FK        | Human factor KBF1<br>mRNA, complete cds                             | 68   | 68T>C   | I23T  |
| M57414  | M57414 | None   | GEN-4FK        | Human neurokinin A<br>receptor (NK-2R) mRNA,<br>complete cds        | 951  | 951G>A  | S     |
| M57414  | M57414 | None   | GEN-4FK        | Human neurokinin A<br>receptor (NK-2R) mRNA,<br>complete cds        | 1171 | 1171C>G | P391A |
| M58525  | M58525 | 116790 | GEN-3S         | complete cds                                                        | 390  | 186T>C  | S     |
| M58525  | M58525 | 116790 | GEN-3S         | Catechol-O-<br>methyltransferase                                    | 390  | 186T>C  | S     |
| M58525  | M58525 | 116790 | GEN-3S         | Catechol-O-<br>methyltransferase                                    | 418  | 214G>T  | A72S  |
| M58525  | M58525 | 116790 | GEN-3S         | Catechol-O-<br>methyltransferase                                    | 423  | 219G>A  | S     |
| M58525  | M58525 | 116790 | GEN-3S         | Catechol-O-<br>methyltransferase                                    | 612  | 408C>G  | S     |
| M58525  | M58525 | 116790 | GEN-3S         | Catechol-O-<br>methyltransferase                                    | 676  | 472A>G  | M158V |
| M58525  | M58525 | 116790 | GEN-3S         | Catechol-O-<br>methyltransferase                                    | 676  | 472A>G  | M158V |
| M58525  | M58525 | 116790 | GEN-3S         | Catechol-O-<br>methyltransferase                                    | 813  | 609C>T  | S     |
| M58525  | M58525 | 116790 | GEN-3S         | Catechol-O-<br>methyltransferase                                    | 1031 | 827delC | F     |
| M58525  | M58525 | 116790 | GEN-3S         | Catechol-O-<br>methyltransferase                                    | 1039 | 835C>A  | 3     |
| M58664  | M58664 | 103000 | GEN-395        | methylyltransferase<br>Homo sapiens CD24 signal<br>transducer mRNA, | 226  | 170C>T  | A57V  |



|        |        |        |         |                                                        |      |         |       |
|--------|--------|--------|---------|--------------------------------------------------------|------|---------|-------|
| M58664 | M58664 | 103000 | GEN-395 | Homo sapiens CD24 signal transducer mRNA, complete cds | 570  | 514A>T  | 3     |
| M58664 | M58664 | 103000 | GEN-395 | Homo sapiens CD24 signal transducer mRNA, complete cds | 1109 | 1053A>G | 3     |
| M58664 | M58664 | 103000 | GEN-395 | Homo sapiens CD24 signal transducer mRNA, complete cds | 1334 | 1278C>G | 3     |
| M58664 | M58664 | 103000 | GEN-395 | Homo sapiens CD24 signal transducer mRNA, complete cds | 1345 | 1289T>C | 3     |
| M58664 | M58664 | 103000 | GEN-395 | Homo sapiens CD24 signal transducer mRNA, complete cds | 1374 | 1318C>T | 3     |
| M58664 | M58664 | 103000 | GEN-395 | Homo sapiens CD24 signal transducer mRNA, complete cds | 1403 | 1347C>T | 3     |
| M58664 | M58664 | 103000 | GEN-395 | Homo sapiens CD24 signal transducer mRNA, complete cds | 1408 | 1352T>G | 3     |
| M58664 | M58664 | 103000 | GEN-395 | Homo sapiens CD24 signal transducer mRNA, complete cds | 1415 | 1359C>A | 3     |
| M58664 | M58664 | 103000 | GEN-395 | Homo sapiens CD24 signal transducer mRNA, complete cds | 1677 | 1621A>G | 3     |
| CD48   | M59904 | 109530 | GEN-3AE | Human pan-leukocyte antigen (CD48) mRNA, complete cds  | 903  | 886T>G  | 3     |
| M59979 | M59979 | 176805 | GEN-Z   | Cyclooxygenase 1 COX1                                  | 644  | 639C>A  | S     |
| M59979 | M59979 | 176805 | GEN-Z   | Cyclooxygenase 1 COX1                                  | 1892 | 1887C>A | 3     |
| M59979 | M59979 | 176805 | GEN-Z   | Cyclooxygenase 1 COX1                                  | 2030 | 2025G>A | 3     |
| M60335 | M60335 | 192225 | GEN-3U  | Vascular cell adhesion molecule 1                      | 1562 | 1463A>G | H488R |
| M60335 | M60335 | 192225 | GEN-3U  | Vascular cell adhesion molecule 1                      | 2178 | 2079C>T | S     |
| M60335 | M60335 | 192225 | GEN-3U  | Vascular cell adhesion molecule 1                      | 2178 | 2079C>T | S     |

|        |        |        |         |                                                              |      |         |       |
|--------|--------|--------|---------|--------------------------------------------------------------|------|---------|-------|
| M60335 | M60335 | 192225 | GEN-3U  | Vascular cell adhesion molecule 1                            | 2196 | 2097T>C | S     |
| M60335 | M60335 | 192225 | GEN-3U  | Vascular cell adhesion molecule 1                            | 2307 | 2208A>G | S     |
| M60335 | M60335 | 192225 | GEN-3U  | Vascular cell adhesion molecule 1                            | 2321 | 2222T>C | 3     |
| TCN2   | M60396 | 275350 | GEN-3AX | Human transcobalamin II (TCII) mRNA, complete cds            | 1164 | 1127C>T | S376L |
| TCN2   | M60396 | 275350 | GEN-3AX | Human transcobalamin II (TCII) mRNA, complete cds            | 1765 | 1728T>C | 3     |
| FPR1   | M60626 | 136537 | GEN-3B5 | Human N-formylpeptide receptor (fMLP-R98) mRNA, complete cds | 1082 | 1037C>A | A346E |
| FPR1   | M60626 | 136537 | GEN-3B5 | Human N-formylpeptide receptor (fMLP-R98) mRNA, complete cds | 1164 | 1119G>C | 3     |
| M60857 | M60857 | 123841 | GEN-10  | Cyclophilin B                                                | 183  | 171C>T  | S     |
| M60857 | M60857 | 123841 | GEN-10  | Cyclophilin B                                                | 217  | 205G>T  | V69L  |
| M60857 | M60857 | 123841 | GEN-10  | Cyclophilin B                                                | 702  | 690C>T  | 3     |
| M60857 | M60857 | 123841 | GEN-10  | Cyclophilin B                                                | 804  | 792A>C  | 3     |
| CD53   | M60871 | 151525 | GEN-3BA | Human cell surface antigen (CD53) mRNA, complete cds         | 645  | 572G>A  | C191Y |
| M61764 | M61764 | 191135 | GEN-FO  | Tubulin, gamma polypeptide                                   | 693  | 669A>G  | S     |
| M61764 | M61764 | 191135 | GEN-FO  | Tubulin, gamma polypeptide                                   | 723  | 699T>C  | S     |
| M61764 | M61764 | 191135 | GEN-FO  | Tubulin, gamma polypeptide                                   | 849  | 825T>G  | S     |
| M61764 | M61764 | 191135 | GEN-FO  | Tubulin, gamma polypeptide                                   | 858  | 834G>A  | S     |
| M61764 | M61764 | 191135 | GEN-FO  | Tubulin, gamma polypeptide                                   | 1033 | 1009T>C | S     |
| M61764 | M61764 | 191135 | GEN-FO  | Tubulin, gamma polypeptide                                   | 1053 | 1029C>G | S     |
| M61764 | M61764 | 191135 | GEN-FO  | Tubulin, gamma polypeptide                                   | 1131 | 1107G>A | S     |
| M61764 | M61764 | 191135 | GEN-FO  | Tubulin, gamma polypeptide                                   | 1188 | 1164C>T | S     |

|        |        |        |         |                                                                  |      |         |       |
|--------|--------|--------|---------|------------------------------------------------------------------|------|---------|-------|
| M64592 | M64592 | 120420 | GEN-3X  | Granulocyte colony-stimulating factor                            | 271  | 271T>G  | Y91D  |
| M64592 | M64592 | 120420 | GEN-3X  | Granulocyte colony-stimulating factor                            | 1533 | 1533C>T | S     |
| M64799 | M64799 | None   | GEN-4DN | Histamine receptor H2                                            | 398  | 398T>C  | V133A |
| M64799 | M64799 | None   | GEN-4DN | Histamine receptor H2                                            | 525  | 525A>T  | K175N |
| M64799 | M64799 | None   | GEN-4DN | Histamine receptor H2                                            | 620  | 620A>G  | K207R |
| M64799 | M64799 | None   | GEN-4DN | Histamine receptor H2                                            | 649  | 649A>G  | N217D |
| M64799 | M64799 | None   | GEN-4DN | Histamine receptor H2                                            | 692  | 692A>G  | K231R |
| M64799 | M64799 | None   | GEN-4DN | Histamine receptor H2                                            | 802  | 802G>A  | V268M |
| C5     | M65134 | 120900 | GEN-3FT | Human complement component C5 mRNA, 3'end                        | 1171 | 1171A>G | I391V |
| EDN2   | M65199 | 131241 | GEN-CBS | Endothelin 2                                                     | 384  | 314C>T  | A105V |
| EDN2   | M65199 | 131241 | GEN-CBS | Endothelin 2                                                     | 997  | 927A>G  | 3     |
| EDN2   | M65199 | 131241 | GEN-CBS | Endothelin 2                                                     | 997  | 927A>G  | 3     |
| M67439 | M67439 | 126453 | GEN-4EI | Dopamine Receptor D5                                             | 1500 | 1353T>A | S     |
| M67439 | M67439 | 126453 | GEN-4EI | Dopamine Receptor D5                                             | 1512 | 1365G>A | F     |
| M67439 | M67439 | 126453 | GEN-4EI | Dopamine Receptor D5                                             | 1566 | 1419G>A | S     |
| M68892 | M68892 | 147559 | GEN-15  | Leukocyte integrin beta-7                                        | 1327 | 1176C>T | S     |
| M69043 | M69043 | 164008 | GEN-3IZ | Homo sapiens MAD-3 mRNA encoding IKB-like activity, complete cds | 400  | 306T>C  | S     |
| M69043 | M69043 | 164008 | GEN-3IZ | Homo sapiens MAD-3 mRNA encoding IKB-like activity, complete cds | 1050 | 956T>C  | 3     |
| M69043 | M69043 | 164008 | GEN-3IZ | Homo sapiens MAD-3 mRNA encoding IKB-like activity, complete cds | 1119 | 1025G>A | 3     |
| M69043 | M69043 | 164008 | GEN-3IZ | Homo sapiens MAD-3 mRNA encoding IKB-like activity, complete cds | 1174 | 1080A>G | 3     |

|        |        |        |         |                                                                        |      |         |       |
|--------|--------|--------|---------|------------------------------------------------------------------------|------|---------|-------|
| M69226 | M69226 | 309850 | GEN-3Z  | Monoamine oxidase A                                                    | 435  | 385A>C  | S     |
| M69226 | M69226 | 309850 | GEN-3Z  | Monoamine oxidase A                                                    | 936  | 886C>T  | F     |
| M69226 | M69226 | 309850 | GEN-3Z  | Monoamine oxidase A                                                    | 941  | 891T>G  | S     |
| M69226 | M69226 | 309850 | GEN-3Z  | Monoamine oxidase A                                                    | 941  | 891T>G  | S     |
| M69226 | M69226 | 309850 | GEN-3Z  | Monoamine oxidase A                                                    | 1076 | 1026A>T | S     |
| M69226 | M69226 | 309850 | GEN-3Z  | Monoamine oxidase A                                                    | 1373 | 1323G>A | F     |
| M69226 | M69226 | 309850 | GEN-3Z  | Monoamine oxidase A                                                    | 1460 | 1410C>T | S     |
| M69226 | M69226 | 309850 | GEN-3Z  | Monoamine oxidase A                                                    | 1460 | 1410C>T | S     |
| M69226 | M69226 | 309850 | GEN-3Z  | Monoamine oxidase A                                                    | 1609 | 1559A>G | K520R |
| M71246 | M71246 | None   | GEN-3KO | Interferon alpha 17                                                    | 131  | 131A>C  | H44P  |
| M71246 | M71246 | None   | GEN-3KO | Interferon alpha 17                                                    | 483  | 483C>T  | S     |
| M71246 | M71246 | None   | GEN-3KO | Interferon alpha 17                                                    | 512  | 512G>T  | R171I |
| M73700 | M73700 | 150210 | GEN-S6  | Human neutrophil lactoferrin mRNA, complete cds and 5' promoter region | 2673 | 85G>A   | A29T  |
| M73700 | M73700 | 150210 | GEN-S6  | Human neutrophil lactoferrin mRNA, complete cds and 5' promoter region | 3090 | 502G>A  | V168M |
| M73700 | M73700 | 150210 | GEN-S6  | Human neutrophil lactoferrin mRNA, complete cds and 5' promoter region | 4101 | 1513G>A | D505N |
| M73700 | M73700 | 150210 | GEN-S6  | Human neutrophil lactoferrin mRNA, complete cds and 5' promoter region | 4211 | 1623T>C | S     |
| M73700 | M73700 | 150210 | GEN-S6  | Human neutrophil lactoferrin mRNA, complete cds and 5' promoter region | 4325 | 1737G>C | E579D |
| M73700 | M73700 | 150210 | GEN-S6  | Human neutrophil lactoferrin mRNA, complete cds and 5' promoter region | 4482 | 1894C>T | S     |
| M74782 | M74782 | 308385 | GEN-64  | Interleukin 3 receptor, alpha                                          | 1396 | 1250C>T | 3     |

|        |        |        |         |                                                                                                     |      |         |        |
|--------|--------|--------|---------|-----------------------------------------------------------------------------------------------------|------|---------|--------|
| CD79B  | M80461 | 147245 | GEN-3UT | (low affinity)<br>Human B29 mRNA,<br>complete cds                                                   | 795  | 781C>T  | 3      |
| CD79B  | M80461 | 147245 | GEN-3UT | Human B29 mRNA,<br>complete cds                                                                     | 804  | 790C>A  | 3      |
| CD79B  | M80461 | 147245 | GEN-3UT | Human B29 mRNA,<br>complete cds                                                                     | 1033 | 1019C>T | 3      |
| M80462 | M80462 | 112205 | GEN-3US | Human MB-1 mRNA,<br>complete cds                                                                    | 241  | 205G>A  | V69I   |
| M80646 | M80646 | 274180 | GEN-40  | Thromboxane synthase                                                                                | 756  | 585G>C  | S      |
| M80646 | M80646 | 274180 | GEN-40  | Thromboxane synthase                                                                                | 1240 | 1069C>G | L357V  |
| CD34   | M81104 | 142230 | GEN-3VN | Human CD34 mRNA,<br>complete cds                                                                    | 1338 | 1045A>G | K349E  |
| CD34   | M81104 | 142230 | GEN-3VN | Human CD34 mRNA,<br>complete cds                                                                    | 2490 | 2197G>A | 3      |
| M81590 | M81590 | 182131 | GEN-3VZ | Serotonin 5-HT receptors<br>5-HT1D                                                                  | 190  | 129C>T  | S      |
| M81590 | M81590 | 182131 | GEN-3VZ | Serotonin 5-HT receptors<br>5-HT1D                                                                  | 432  | 371T>G  | F124C  |
| M81590 | M81590 | 182131 | GEN-3VZ | Serotonin 5-HT receptors<br>5-HT1D                                                                  | 922  | 861G>C  | S      |
| M81590 | M81590 | 182131 | GEN-3VZ | Serotonin 5-HT receptors<br>5-HT1D                                                                  | 1241 | 1180G>A | 3      |
| M81695 | M81695 | 151510 | GEN-17  | Leukocyte integrin alpha-x                                                                          | 1834 | 1770G>C | S      |
| M81695 | M81695 | 151510 | GEN-17  | Leukocyte integrin alpha-x                                                                          | 3282 | 3218C>T | T1073M |
| M81695 | M81695 | 151510 | GEN-17  | Leukocyte integrin alpha-x                                                                          | 4213 | 4149C>G | 3      |
| TAC1R  | M81797 | 162323 | GEN-3W8 | Tachylinins NK1 receptor                                                                            | 696  | 652G>A  | V218I  |
| TAC1R  | M81797 | 162323 | GEN-3W8 | Tachylinins NK1 receptor                                                                            | 1397 | 1353G>C | 3      |
| M83566 | M83566 | 114206 | GEN-3Y7 | Human<br>neuroendocrine/beta-cell-<br>type calcium channel<br>alpha-1 subunit mRNA,<br>complete cds | 1222 | 1104C>T | S      |
| M83566 | M83566 | 114206 | GEN-3Y7 | Human<br>neuroendocrine/beta-cell-<br>type calcium channel<br>alpha-1 subunit mRNA,<br>complete cds | 1468 | 1350G>A | S      |

|        |        |        |         |                                                                      |      |         |       |
|--------|--------|--------|---------|----------------------------------------------------------------------|------|---------|-------|
| CHRNA5 | M83712 | 118505 | GEN-3YQ | Nicotinic, Cholinergic receptor alpha 5                              | 1340 | 1192G>A | D398N |
| M84379 | M84379 | 142800 | GEN-SA  | Human MHC class I lymphocyte antigen (HLA-A 0201) mRNA, complete cds | 28   | 28G>C   | V10L  |
| M84379 | M84379 | 142800 | GEN-SA  | Human MHC class I lymphocyte antigen (HLA-A 0201) mRNA, complete cds | 98   | 98T>A   | F33Y  |
| M84379 | M84379 | 142800 | GEN-SA  | Human MHC class I lymphocyte antigen (HLA-A 0201) mRNA, complete cds | 102  | 102A>C  | S     |
| M84379 | M84379 | 142800 | GEN-SA  | Human MHC class I lymphocyte antigen (HLA-A 0201) mRNA, complete cds | 144  | 144A>C  | S     |
| M84379 | M84379 | 142800 | GEN-SA  | Human MHC class I lymphocyte antigen (HLA-A 0201) mRNA, complete cds | 240  | 240T>G  | S     |
| M84379 | M84379 | 142800 | GEN-SA  | Human MHC class I lymphocyte antigen (HLA-A 0201) mRNA, complete cds | 257  | 257G>A  | G86E  |
| M84379 | M84379 | 142800 | GEN-SA  | Human MHC class I lymphocyte antigen (HLA-A 0201) mRNA, complete cds | 292  | 292C>G  | H98D  |
| M84379 | M84379 | 142800 | GEN-SA  | Human MHC class I lymphocyte antigen (HLA-A 0201) mRNA, complete cds | 362  | 362G>T  | R121M |
| M84379 | M84379 | 142800 | GEN-SA  | Human MHC class I lymphocyte antigen (HLA-A 0201) mRNA, complete cds | 391  | 391T>G  | W131G |
| M84379 | M84379 | 142800 | GEN-SA  | Human MHC class I lymphocyte antigen (HLA-A 0201) mRNA, complete cds | 418  | 418T>G  | Y140D |

|        |        |        |        |                                                                                |     |        |       |
|--------|--------|--------|--------|--------------------------------------------------------------------------------|-----|--------|-------|
| M84379 | M84379 | 142800 | GEN-SA | Human MHC class I<br>lymphocyte antigen (HLA-<br>A 0201) mRNA, complete<br>cds | 453 | 453A>C | K151N |
| M84379 | M84379 | 142800 | GEN-SA | Human MHC class I<br>lymphocyte antigen (HLA-<br>A 0201) mRNA, complete<br>cds | 527 | 527T>A | V176E |
| M84379 | M84379 | 142800 | GEN-SA | Human MHC class I<br>lymphocyte antigen (HLA-<br>A 0201) mRNA, complete<br>cds | 539 | 539T>G | L180W |
| M84379 | M84379 | 142800 | GEN-SA | Human MHC class I<br>lymphocyte antigen (HLA-<br>A 0201) mRNA, complete<br>cds | 622 | 622G>C | A208P |
| M84379 | M84379 | 142800 | GEN-SA | Human MHC class I<br>lymphocyte antigen (HLA-<br>A 0201) mRNA, complete<br>cds | 630 | 630A>G | S     |
| M84379 | M84379 | 142800 | GEN-SA | Human MHC class I<br>lymphocyte antigen (HLA-<br>A 0201) mRNA, complete<br>cds | 666 | 666A>G | S     |
| M84379 | M84379 | 142800 | GEN-SA | Human MHC class I<br>lymphocyte antigen (HLA-<br>A 0201) mRNA, complete<br>cds | 762 | 762C>T | S     |
| M84379 | M84379 | 142800 | GEN-SA | Human MHC class I<br>lymphocyte antigen (HLA-<br>A 0201) mRNA, complete<br>cds | 789 | 789A>G | S     |
| M84379 | M84379 | 142800 | GEN-SA | Human MHC class I<br>lymphocyte antigen (HLA-<br>A 0201) mRNA, complete<br>cds | 806 | 806C>T | A269V |
| M84379 | M84379 | 142800 | GEN-SA | Human MHC class I<br>lymphocyte antigen (HLA-<br>A 0201) mRNA, complete<br>cds | 807 | 807G>A | S     |

|        |        |        |        |                                                                                |     |        |       |
|--------|--------|--------|--------|--------------------------------------------------------------------------------|-----|--------|-------|
| M84379 | M84379 | 142800 | GEN-SA | Human MHC class I<br>lymphocyte antigen (HLA-<br>A 0201) mRNA, complete<br>cgs | 808 | 808G>T | A270S |
| M84379 | M84379 | 142800 | GEN-SA | Human MHC class I<br>lymphocyte antigen (HLA-<br>A 0201) mRNA, complete<br>cgs | 819 | 819G>A | S     |
| M84379 | M84379 | 142800 | GEN-SA | Human MHC class I<br>lymphocyte antigen (HLA-<br>A 0201) mRNA, complete<br>cgs | 829 | 829C>G | Q277E |
| M84379 | M84379 | 142800 | GEN-SA | Human MHC class I<br>lymphocyte antigen (HLA-<br>A 0201) mRNA, complete<br>cgs | 868 | 868T>C | S     |
| M84379 | M84379 | 142800 | GEN-SA | Human MHC class I<br>lymphocyte antigen (HLA-<br>A 0201) mRNA, complete<br>cgs | 870 | 870G>C | L290F |
| M84379 | M84379 | 142800 | GEN-SA | Human MHC class I<br>lymphocyte antigen (HLA-<br>A 0201) mRNA, complete<br>cgs | 900 | 900G>A | S     |
| M84379 | M84379 | 142800 | GEN-SA | Human MHC class I<br>lymphocyte antigen (HLA-<br>A 0201) mRNA, complete<br>cgs | 901 | 901T>G | S301A |
| M84379 | M84379 | 142800 | GEN-SA | Human MHC class I<br>lymphocyte antigen (HLA-<br>A 0201) mRNA, complete<br>cgs | 916 | 916A>G | I306V |
| M84379 | M84379 | 142800 | GEN-SA | Human MHC class I<br>lymphocyte antigen (HLA-<br>A 0201) mRNA, complete<br>cgs | 945 | 945G>A | S     |
| M84379 | M84379 | 142800 | GEN-SA | Human MHC class I<br>lymphocyte antigen (HLA-<br>A 0201) mRNA, complete<br>cgs | 952 | 952T>C | F318L |
| M84379 | M84379 | 142800 | GEN-SA | Human MHC class I<br>lymphocyte antigen (HLA-<br>A 0201) mRNA, complete<br>cgs | 967 | 967A>G | T323A |



|        |        |        |         |                                                                      |      |         |       |
|--------|--------|--------|---------|----------------------------------------------------------------------|------|---------|-------|
| M84379 | M84379 | 142800 | GEN-SA  | lymphocyte antigen (HLA-A 0201) mRNA, complete cds                   | 987  | 987T>C  | S     |
| M84379 | M84379 | 142800 | GEN-SA  | Human MHC class I lymphocyte antigen (HLA-A 0201) mRNA, complete cds | 992  | 992T>G  | M331R |
| M84379 | M84379 | 142800 | GEN-SA  | Human MHC class I lymphocyte antigen (HLA-A 0201) mRNA, complete cds | 1005 | 1005G>C | K335N |
| M84379 | M84379 | 142800 | GEN-SA  | Human MHC class I lymphocyte antigen (HLA-A 0201) mRNA, complete cds | 1013 | 1013A>G | D338G |
| M84379 | M84379 | 142800 | GEN-SA  | Human MHC class I lymphocyte antigen (HLA-A 0201) mRNA, complete cds | 1029 | 1029C>T | S     |
| M84379 | M84379 | 142800 | GEN-SA  | Human MHC class I lymphocyte antigen (HLA-A 0201) mRNA, complete cds | 1033 | 1033T>A | S345T |
| M84379 | M84379 | 142800 | GEN-SA  | Human MHC class I lymphocyte antigen (HLA-A 0201) mRNA, complete cds | 1072 | 1072G>A | V358M |
| M84526 | M84526 | 134350 | GEN-3ZL | Human adipsin/complement factor D mRNA, complete cds                 | 46   | (-9)C>T | 5     |
| M84526 | M84526 | 134350 | GEN-3ZL | Human adipsin/complement factor D mRNA, complete cds                 | 399  | 345C>A  | S     |
| M84526 | M84526 | 134350 | GEN-3ZL | Human adipsin/complement factor D mRNA, complete cds                 | 408  | 354A>G  | S     |
| M84526 | M84526 | 134350 | GEN-3ZL | Human adipsin/complement factor D mRNA, complete cds                 | 859  | 805C>T  | 3     |

|        |        |        |         |                                                                      |       |      |                  |       |
|--------|--------|--------|---------|----------------------------------------------------------------------|-------|------|------------------|-------|
| M84526 | M84526 | 134350 | 3ZL     | adipsin/complement factor D mRNA, complete cds                       | Human | 891  | 837G>C           | 3     |
| M84747 | M84747 | 300007 | GEN-3ZL | adipsin/complement factor D mRNA, complete cds                       |       | 1273 | 1094G>A          | R365H |
| TGFBR2 | M85079 | 190182 | GEN-3ZS | Human TGF-beta type II receptor mRNA, complete cds                   |       | 2045 | 1710A>C          | 3     |
| YWHAZ  | M86400 | 601288 | GEN-40Y | Human phospholipase A2 mRNA, complete cds                            |       | 1653 | 1569T>A          | 3     |
| YWHAZ  | M86400 | 601288 | GEN-40Y | Human phospholipase A2 mRNA, complete cds                            |       | 2599 | 2515C>G          | 3     |
| YWHAZ  | M86400 | 601288 | GEN-40Y | Human phospholipase A2 mRNA, complete cds                            |       | 2619 | 2535A>C          | 3     |
| YWHAZ  | M86400 | 601288 | GEN-40Y | Human phospholipase A2 mRNA, complete cds                            |       | 2656 | 2572A>C          | 3     |
| YWHAZ  | M86400 | 601288 | GEN-40Y | Human phospholipase A2 mRNA, complete cds                            |       | 2745 | 2661C>T          | 3     |
| YWHAZ  | M86400 | 601288 | GEN-40Y | Human phospholipase A2 mRNA, complete cds                            |       | 2761 | 2677A>C          | 3     |
| M86511 | M86511 | 158120 | GEN-419 | Human monocyte antigen CD14 (CD14) mRNA, complete cds                |       | 1142 | 1067C>A          | T356N |
| M86511 | M86511 | 158120 | GEN-419 | Human monocyte antigen CD14 (CD14) mRNA, complete cds                |       | 1176 | 1101G>C          | S     |
| M87503 | M87503 | None   | GEN-443 | Human IFN-responsive transcription factor subunit mRNA, complete cds |       | 1424 | 1390T>A          | 3     |
| M87503 | M87503 | None   | GEN-443 | Human IFN-responsive transcription factor subunit mRNA, complete cds |       | 1524 | 1490A>C          | 3     |
| M89473 | M89473 | None   | GEN-4FU | NEUROMEDIN K RECEPTOR                                                |       | 1614 | 1471T>C          | 3     |
| M90100 | M90100 | 600262 | GEN-1A  | Cyclooxygenase 2 COX2                                                |       | 2159 | 2062G>C          | 3     |
| M90100 | M90100 | 600262 | GEN-1A  | Cyclooxygenase 2 COX2                                                |       | 2186 | 2089-2094ATATTA  | 3     |
| M90100 | M90100 | 600262 | GEN-1A  | Cyclooxygenase 2 COX2                                                |       | 2186 | 2089-2094delATAT | 3     |

|        |        |        |         |                                                          |      |         |        |
|--------|--------|--------|---------|----------------------------------------------------------|------|---------|--------|
| M90100 | M90100 | 600262 | GEN-1A  | Cyclooxygenase 2 COX2                                    | 2230 | 2133A>G | 3      |
| M90100 | M90100 | 600262 | GEN-1A  | Cyclooxygenase 2 COX2                                    | 2339 | 2242T>C | 3      |
| M90100 | M90100 | 600262 | GEN-1A  | Cyclooxygenase 2 COX2                                    | 2409 | 2312G>A | 3      |
| M90100 | M90100 | 600262 | GEN-1A  | Cyclooxygenase 2 COX2                                    | 2726 | 2629C>T | 3      |
| M90100 | M90100 | 600262 | GEN-1A  | Cyclooxygenase 2 COX2                                    | 2983 | 2886C>T | 3      |
| M92269 | M92269 | 114205 | GEN-SV  | Ca Channel alpha1c (alt. splice) L-Type                  | 3846 | 3846C>T | S      |
| M92269 | M92269 | 114205 | GEN-SV  | Ca Channel alpha1c (alt. splice) L-Type                  | 5505 | 5505G>A | S      |
| M92269 | M92269 | 114205 | GEN-SV  | Ca Channel alpha1c (alt. splice) L-Type                  | 6582 | 6582A>G | S      |
| M92269 | M92269 | 114205 | GEN-SV  | Ca Channel alpha1c (alt. splice) L-Type                  | 6613 | 6613G>C | G2205R |
| M92269 | M92269 | 114205 | GEN-SV  | Ca Channel alpha1c (alt. splice) L-Type                  | 6614 | 6614G>C | G2205A |
| M92303 | M92303 | 114207 | GEN-1C  | L-Type voltage sensitive channel beta-1                  | 860  | 711G>A  | S      |
| IL8RB  | M94582 | 146928 | GEN-49G | Interleukin 8 receptor                                   | 838  | 786T>C  | S      |
| IL8RB  | M94582 | 146928 | GEN-49G | Interleukin 8 receptor                                   | 1262 | 1210C>T | 3      |
| IL8RB  | M94582 | 146928 | GEN-49G | Interleukin 8 receptor                                   | 1494 | 1442A>G | 3      |
| M95678 | M95678 | 604114 | GEN-4A6 | Homo sapiens phospholipase C-beta-2 mRNA, complete cds   | 1346 | 1182T>C | S      |
| M95678 | M95678 | 604114 | GEN-4A6 | Homo sapiens phospholipase C-beta-2 mRNA, complete cds   | 3436 | 3272A>G | E1091G |
| M95678 | M95678 | 604114 | GEN-4A6 | Homo sapiens phospholipase C-beta-2 mRNA, complete cds   | 4137 | 3973C>T | 3      |
| M95708 | M95708 | 107271 | GEN-SF  | Homo sapiens Ly-6-like protein (CD59) mRNA, complete cds | 497  | 435C>T  | 3      |
| M96652 | M96652 | 147851 | GEN-65  | Interleukin 5 receptor alpha                             | 883  | 634T>G  | S212A  |
| M96954 | M96954 | 603413 | GEN-4B5 | Homo sapiens nucleolysin TIAR mRNA, complete cds         | 957  | 912A>C  | Q304H  |
| ID2    | M97796 | 600386 | GEN-    | Human helix-loop-helix                                   | 402  | 294C>G  | S      |

|        |        |        |         |         |                                                                                           |      |         |       |
|--------|--------|--------|---------|---------|-------------------------------------------------------------------------------------------|------|---------|-------|
| M98045 | M98045 | 136510 | GEN-4C3 | 4C0     | protein (ld-2) mRNA, complete cds                                                         | 802  | 732C>T  | S     |
| M98045 | M98045 | 136510 | GEN-4C3 | GEN-4C3 | Homo sapiens folypolyglutamate synthetase mRNA, complete cds                              | 1747 | 1677G>T | 3     |
| M98045 | M98045 | 136510 | GEN-4C3 | GEN-4C3 | Homo sapiens folypolyglutamate synthetase mRNA, complete cds                              | 1900 | 1830T>C | 3     |
| M98045 | M98045 | 136510 | GEN-4C3 | GEN-4C3 | Homo sapiens folypolyglutamate synthetase mRNA, complete cds                              | 1900 | 1830T>C | 3     |
| M98045 | M98045 | 136510 | GEN-4C3 | GEN-4C3 | Homo sapiens folypolyglutamate synthetase mRNA, complete cds                              | 1912 | 1842G>A | 3     |
| M98045 | M98045 | 136510 | GEN-4C3 | GEN-4C3 | Homo sapiens folypolyglutamate synthetase mRNA, complete cds                              | 1995 | 1925C>G | 3     |
| S46622 | S46622 | 114107 | GEN-1F  | GEN-1F  | Calcineurin A-gamma                                                                       | 1893 | 1607C>G | 3     |
| S46622 | S46622 | 114107 | GEN-1F  | GEN-1F  | Calcineurin A-gamma                                                                       | 1941 | 1655A>G | 3     |
| S57235 | S57235 | 153634 | GEN-37N | GEN-37N | CD68=110kda transmembrane glycoprotein [human, promonocyte cell line U937, mRNA, 1722 nt] | 775  | 760A>C  | K254Q |
| U00672 | U00672 | 146933 | GEN-4A  | GEN-4A  | Interleukin 10 receptor                                                                   | 3377 | 3316A>C | 3     |
| U00672 | U00672 | 146933 | GEN-4A  | GEN-4A  | Interleukin 10 receptor                                                                   | 3524 | 3463A>G | 3     |
| U02882 | U02882 | 600129 | GEN-XU  | GEN-XU  | Human rolipram-sensitive 3,5-cyclic AMP phosphodiesterase mRNA, complete cds              | 1798 | 1690T>C | C564R |
| U02882 | U02882 | 600129 | GEN-XU  | GEN-XU  | Human rolipram-sensitive 3,5-cyclic AMP                                                   | 1881 | 1773G>A | S     |

|        |        |        |         |                                                                                                                                                             |      |         |       |
|--------|--------|--------|---------|-------------------------------------------------------------------------------------------------------------------------------------------------------------|------|---------|-------|
| U02882 | U02882 | 600129 | GEN-XU  | phosphodiesterase mRNA,<br>complete cds                                                                                                                     | 4691 | 4583T>G | 3     |
| U03858 | U03858 | 600007 | GEN-MDM | Human rolipram-sensitive<br>3,5-cyclic AMP<br>phosphodiesterase mRNA,<br>complete cds                                                                       | 683  | 600C>T  | S     |
| U03858 | U03858 | 600007 | GEN-MDM | Fms-related tyrosine<br>kinase 3 ligand                                                                                                                     | 1016 | 933T>C  | 3     |
| U03882 | U03882 | 601267 | GEN-12B | Fms-related tyrosine<br>kinase 3 ligand<br>Human monocyte<br>chemoattractant protein 1<br>receptor (MCP-1RA)<br>alternatively spliced<br>mRNA, complete cds | 1436 | 1397G>A | 3     |
| DDH1   | U05598 | 600450 | GEN-184 | Human dihydrodiol<br>dehydrogenase mRNA,<br>complete cds                                                                                                    | 38   | 15C>T   | S     |
| DDH1   | U05598 | 600450 | GEN-184 | Human dihydrodiol<br>dehydrogenase mRNA,<br>complete cds                                                                                                    | 282  | 259A>T  | S87C  |
| DDH1   | U05598 | 600450 | GEN-184 | Human dihydrodiol<br>dehydrogenase mRNA,<br>complete cds                                                                                                    | 350  | 327C>T  | S     |
| DDH1   | U05598 | 600450 | GEN-184 | Human dihydrodiol<br>dehydrogenase mRNA,<br>complete cds                                                                                                    | 365  | 342T>C  | S     |
| DDH1   | U05598 | 600450 | GEN-184 | Human dihydrodiol<br>dehydrogenase mRNA,<br>complete cds                                                                                                    | 464  | 441G>A  | S     |
| DDH1   | U05598 | 600450 | GEN-184 | Human dihydrodiol<br>dehydrogenase mRNA,<br>complete cds                                                                                                    | 474  | 451A>G  | M151V |
| DDH1   | U05598 | 600450 | GEN-184 | Human dihydrodiol<br>dehydrogenase mRNA,<br>complete cds                                                                                                    | 532  | 509A>G  | H170R |
| DDH1   | U05598 | 600450 | GEN-184 | Human dihydrodiol<br>dehydrogenase mRNA,<br>complete cds                                                                                                    | 538  | 515T>A  | L172Q |
| DDH1   | U05598 | 600450 | GEN-184 | Human dihydrodiol<br>dehydrogenase mRNA,<br>complete cds                                                                                                    | 689  | 666T>C  | S     |

|        |        |        |         |                                                                                            |      |         |       |
|--------|--------|--------|---------|--------------------------------------------------------------------------------------------|------|---------|-------|
| DDH1   | U05598 | 600450 | GEN-184 | complete cds<br>Human dihydrodiol<br>dehydrogenase mRNA,                                   | 806  | 783G>A  | S     |
| DDH1   | U05598 | 600450 | GEN-184 | complete cds<br>Human dihydrodiol<br>dehydrogenase mRNA,                                   | 872  | 849G>T  | S     |
| DDH1   | U05598 | 600450 | GEN-184 | complete cds<br>Human dihydrodiol<br>dehydrogenase mRNA,                                   | 952  | 929T>G  | I310S |
| DDH1   | U05598 | 600450 | GEN-184 | complete cds<br>Human dihydrodiol<br>dehydrogenase mRNA,                                   | 1020 | 997G>A  | 3     |
| DDH1   | U05598 | 600450 | GEN-184 | complete cds<br>Human dihydrodiol<br>dehydrogenase mRNA,                                   | 1035 | 1012G>A | 3     |
| DDH1   | U05598 | 600450 | GEN-184 | complete cds<br>Human dihydrodiol<br>dehydrogenase mRNA,                                   | 1112 | 1089C>T | 3     |
| U05875 | U05875 | 147569 | GEN-18J | complete cds<br>Human clone pSK1<br>interferon gamma receptor<br>accessory factor-1 (AF-1) | 2047 | 1399C>G | 3     |
| U05875 | U05875 | 147569 | GEN-18J | complete cds<br>Human clone pSK1<br>interferon gamma receptor<br>accessory factor-1 (AF-1) | 2087 | 1439T>C | 3     |
| XDH    | U06117 | 278300 | GEN-194 | mRNA, complete cds<br>Human xanthine<br>dehydrogenase (XDH)                                | 3951 | 3888C>G | S     |
| U07225 | U07225 | 600041 | GEN-1DM | mRNA, complete cds<br>P2Y2 purinoceptor                                                    | 2008 | 1763G>A | 3     |
| U07989 | U07989 | None   | GEN-Q2  | Human Burkitts lymphoma<br>immunoglobulin kappa light<br>chain mRNA, partial cds           | 39   | 39T>A   | S     |
| U07989 | U07989 | None   | GEN-Q2  | Human Burkitts lymphoma<br>immunoglobulin kappa light<br>chain mRNA, partial cds           | 307  | 307G>C  | V103L |
| U07989 | U07989 | None   | GEN-Q2  | Human Burkitts lymphoma<br>immunoglobulin kappa light<br>chain mRNA, partial cds           | 312  | 312A>G  | S     |

|         |        |        |         |                                                                            |      |         |       |
|---------|--------|--------|---------|----------------------------------------------------------------------------|------|---------|-------|
| U07989  | U07989 | None   | GEN-Q2  | Human Burkitts lymphoma immunoglobulin kappa light chain mRNA, partial cds | 568  | 568G>C  | V190L |
| U07989  | U07989 | None   | GEN-Q2  | Human Burkitts lymphoma immunoglobulin kappa light chain mRNA, partial cds | 610  | 610G>A  | V204I |
| U08015  | U08015 | 600489 | GEN-1FD | Human NF-ATc mRNA, complete cds                                            | 530  | 291C>T  | S     |
| U08015  | U08015 | 600489 | GEN-1FD | Human NF-ATc mRNA, complete cds                                            | 1094 | 855G>A  | S     |
| U08015  | U08015 | 600489 | GEN-1FD | Human NF-ATc mRNA, complete cds                                            | 2222 | 1983G>A | S     |
| U08015  | U08015 | 600489 | GEN-1FD | Human NF-ATc mRNA, complete cds                                            | 2225 | 1986A>G | S     |
| U08015  | U08015 | 600489 | GEN-1FD | Human NF-ATc mRNA, complete cds                                            | 2295 | 2056A>C | S686R |
| U09117  | U09117 | 602142 | GEN-1GC | Phospholipase C delta-1                                                    | 333  | 239G>A  | R80H  |
| U09117  | U09117 | 602142 | GEN-1GC | Phospholipase C delta-1                                                    | 460  | 366G>A  | S     |
| U09117  | U09117 | 602142 | GEN-1GC | Phospholipase C delta-1                                                    | 1858 | 1764G>A | S     |
| SLC18A3 | U09210 | 600336 | GEN-4F3 | Human vesicular acetylcholine transporter mRNA, complete cds               | 838  | 396T>C  | S     |
| SLC18A3 | U09210 | 600336 | GEN-4F3 | Human vesicular acetylcholine transporter mRNA, complete cds               | 1369 | 927A>G  | S     |
| SLC18A3 | U09210 | 600336 | GEN-4F3 | Human vesicular acetylcholine transporter mRNA, complete cds               | 1567 | 1125C>G | S     |
| SLC18A3 | U09210 | 600336 | GEN-4F3 | Human vesicular acetylcholine transporter mRNA, complete cds               | 2080 | 1638G>T | 3     |
| SLC18A3 | U09210 | 600336 | GEN-4F3 | Human vesicular acetylcholine transporter mRNA, complete cds               | 2199 | 1757G>A | 3     |
| SLC18A3 | U09210 | 600336 | GEN-4F3 | Human vesicular acetylcholine transporter mRNA, complete cds               | 2349 | 1907G>T | 3     |
| U09607  | U09607 | 600173 | GEN-    | Janus kinase 3 (a protein                                                  | 1925 | 1830G>A | M610I |

|        |        |        |         |                                                             |      |         |       |
|--------|--------|--------|---------|-------------------------------------------------------------|------|---------|-------|
| U09759 | U09759 | 602896 | GEN-1HA | tyrosine kinase, leukocyte)                                 | 303  | 152A>G  | N51S  |
| U09759 | U09759 | 602896 | GEN-1HA | Human protein kinase (JNK2) mRNA, complete cds              | 1079 | 928A>G  | I310V |
| U09759 | U09759 | 602896 | GEN-1HA | Human protein kinase (JNK2) mRNA, complete cds              | 1280 | 1129C>T | P377S |
| U09759 | U09759 | 602896 | GEN-1HA | Human protein kinase (JNK2) mRNA, complete cds              | 1559 | 1408C>T | 3     |
| U09806 | U09806 | None   | GEN-4FZ | Human methylenetetrahydrofolate reductase mRNA, partial cds | 120  | 120T>C  | S     |
| U09806 | U09806 | None   | GEN-4FZ | Human methylenetetrahydrofolate reductase mRNA, partial cds | 473  | 473G>A  | R158Q |
| U09806 | U09806 | None   | GEN-4FZ | Human methylenetetrahydrofolate reductase mRNA, partial cds | 550  | 550C>T  | F     |
| U09806 | U09806 | None   | GEN-4FZ | Human methylenetetrahydrofolate reductase mRNA, partial cds | 668  | 668C>T  | A223V |
| U09806 | U09806 | None   | GEN-4FZ | Human methylenetetrahydrofolate reductase mRNA, partial cds | 1059 | 1059T>C | S     |
| U09806 | U09806 | None   | GEN-4FZ | Human methylenetetrahydrofolate reductase mRNA, partial cds | 1289 | 1289C>A | E430A |
| U09806 | U09806 | None   | GEN-4FZ | Human methylenetetrahydrofolate reductase mRNA, partial cds | 1308 | 1308T>C | 3     |



|        |        |        |         |                                                                  |      |         |       |
|--------|--------|--------|---------|------------------------------------------------------------------|------|---------|-------|
| OPRD1  | U10504 | 165195 | GEN-4F5 | Human delta opiate receptor mRNA, complete cds                   | 921  | 921T>C  | S     |
| U11276 | U11276 | 602890 | GEN-1K3 | Human hNKR-P1a protein (NKR-P1A) mRNA, complete cds              | 563  | 503T>C  | I168T |
| TPMT   | U12387 | 187680 | GEN-1LY | Human thiopurine methyltransferase (TPMT) mRNA, complete cds     | 536  | 460G>A  | A154T |
| TPMT   | U12387 | 187680 | GEN-1LY | Human thiopurine methyltransferase (TPMT) mRNA, complete cds     | 795  | 719A>G  | Y240C |
| TPMT   | U12387 | 187680 | GEN-1LY | Human thiopurine methyltransferase (TPMT) mRNA, complete cds     | 1085 | 1009T>C | 3     |
| TPMT   | U12387 | 187680 | GEN-1LY | Human thiopurine methyltransferase (TPMT) mRNA, complete cds     | 1336 | 1260C>T | 3     |
| TPMT   | U12387 | 187680 | GEN-1LY | Human thiopurine methyltransferase (TPMT) mRNA, complete cds     | 1373 | 1297G>A | 3     |
| U12507 | U12507 | 600681 | GEN-1MD | Cardiac inward rectifier potassium channel (HH-IRK1)             | 338  | 13C>A   | S     |
| U12507 | U12507 | 600681 | GEN-1MD | Cardiac inward rectifier potassium channel (HH-IRK1)             | 1597 | 1272G>A | S     |
| U12597 | U12597 | 601895 | GEN-4E  | tumor necrosis factor type 2 receptor associated protein (TRAP3) | 2182 | 2128G>T | 3     |
| U13737 | U13737 | 600636 | GEN-1PC | Human cysteine protease CPP32 isoform alpha mRNA, complete cds   | 2356 | 2132A>C | 3     |
| U13737 | U13737 | 600636 | GEN-1PC | Human cysteine protease CPP32 isoform alpha mRNA, complete cds   | 2535 | 2311C>T | 3     |
| U14510 | U14510 | 602698 | GEN-1RD | Human transcription factor NFATx mRNA, complete cds              | 2128 | 2104A>C | M702L |
| U14510 | U14510 | 602698 | GEN-1RD | Human transcription factor NFATx mRNA, complete cds              | 2516 | 2492T>G | L831W |

|        |        |        |             |                                                                         |      |         |       |
|--------|--------|--------|-------------|-------------------------------------------------------------------------|------|---------|-------|
| U14510 | U14510 | 602698 | GEN-<br>1RD | Human transcription factor<br>NFATx mRNA, complete<br>cds               | 2720 | 2696C>G | A899G |
| U14510 | U14510 | 602698 | GEN-<br>1RD | Human transcription factor<br>NFATx mRNA, complete<br>cds               | 2792 | 2768C>T | A923V |
| U14510 | U14510 | 602698 | GEN-<br>1RD | Human transcription factor<br>NFATx mRNA, complete<br>cds               | 2828 | 2804C>G | A935G |
| U14510 | U14510 | 602698 | GEN-<br>1RD | Human transcription factor<br>NFATx mRNA, complete<br>cds               | 2903 | 2879C>G | A960G |
| U14510 | U14510 | 602698 | GEN-<br>1RD | Human transcription factor<br>NFATx mRNA, complete<br>cds               | 2967 | 2943G>A | S     |
| U14510 | U14510 | 602698 | GEN-<br>1RD | Human transcription factor<br>NFATx mRNA, complete<br>cds               | 3333 | 3309G>A | 3     |
| U14510 | U14510 | 602698 | GEN-<br>1RD | Human transcription factor<br>NFATx mRNA, complete<br>cds               | 3577 | 3553G>A | 3     |
| U14650 | U14650 | 602243 | GEN-<br>1RL | Human platelet-endothelial<br>tetraspan antigen 3 mRNA,<br>complete cds | 638  | 579A>G  | S     |
| U14650 | U14650 | 602243 | GEN-<br>1RL | Human platelet-endothelial<br>tetraspan antigen 3 mRNA,<br>complete cds | 1048 | 989G>A  | 3     |
| U14650 | U14650 | 602243 | GEN-<br>1RL | Human platelet-endothelial<br>tetraspan antigen 3 mRNA,<br>complete cds | 1171 | 1112T>C | 3     |
| U14650 | U14650 | 602243 | GEN-<br>1RL | Human platelet-endothelial<br>tetraspan antigen 3 mRNA,<br>complete cds | 1263 | 1204G>C | 3     |
| U14650 | U14650 | 602243 | GEN-<br>1RL | Human platelet-endothelial<br>tetraspan antigen 3 mRNA,<br>complete cds | 1301 | 1242C>T | 3     |
| U14650 | U14650 | 602243 | GEN-<br>1RL | Human platelet-endothelial<br>tetraspan antigen 3 mRNA,<br>complete cds | 1351 | 1292T>C | 3     |
| U14650 | U14650 | 602243 | GEN-<br>1RL | Human platelet-endothelial<br>tetraspan antigen 3 mRNA,<br>complete cds | 1389 | 1330A>T | 3     |

|        |        |        |         |                                                                               |      |          |       |
|--------|--------|--------|---------|-------------------------------------------------------------------------------|------|----------|-------|
| U14650 | U14650 | 602243 | GEN-1RL | tetraspan antigen 3 mRNA, complete cds                                        | 1404 | 1345G>A  | 3     |
| U15637 | U15637 | 601896 | GEN-1U8 | Human platelet-endothelial tetraspan antigen 3 mRNA, complete cds             | 596  | 386T>C   | M129T |
| U15637 | U15637 | 601896 | GEN-1U8 | Human CD40 binding protein (CD40bp) mRNA, complete cds                        | 1317 | 1107C>T  | S     |
| U16031 | U16031 | None   | GEN-HX  | Human CD40 binding protein (CD40bp) mRNA, complete cds                        | 2964 | 2799G>A  | 3     |
| SDF1   | U16752 | 600835 | GEN-1YK | Transcription Factor IL-4 Stat                                                | 47   | (-34)C>T | 5     |
| SDF1   | U16752 | 600835 | GEN-1YK | Human cytokine SDF-1-beta mRNA, complete cds                                  | 2927 | 2847G>C  | 3     |
| SDF1   | U16752 | 600835 | GEN-1YK | Human cytokine SDF-1-beta mRNA, complete cds                                  | 3159 | 3079T>C  | 3     |
| SDF1   | U16752 | 600835 | GEN-1YK | Human cytokine SDF-1-beta mRNA, complete cds                                  | 3294 | 3214T>G  | 3     |
| NOS1   | U17327 | 163731 | GEN-209 | Human cytokine SDF-1-beta mRNA, complete cds                                  | 3391 | 2706C>T  | S     |
| PDE4A  | U18087 | 600126 | GEN-214 | Human neuronal nitric oxide synthase (NOS1) mRNA, complete cds                | 642  | 633T>G   | S     |
| PDE4A  | U18087 | 600126 | GEN-214 | Human 3,5-cyclic AMP phosphodiesterase HPDE4A6 mRNA, complete cds             | 804  | 795T>C   | S     |
| PDE4A  | U18087 | 600126 | GEN-214 | Human 3,5-cyclic AMP phosphodiesterase HPDE4A6 mRNA, complete cds             | 1616 | 1607A>C  | E536A |
| U18242 | U18242 | 601118 | GEN-1N  | Human 3,5-cyclic AMP phosphodiesterase HPDE4A6 mRNA, complete cds             | 1117 | 1081T>G  | 3     |
| U19487 | U19487 | 176804 | GEN-4I  | Cyclophilin Ligand (calcium modulating) PROTAGLANDIN E2 RECEPTOR, EP2 SUBTYPE | 85   | (-72)A>G | 5     |

|        |        |        |             |                                                                            |      |                   |       |
|--------|--------|--------|-------------|----------------------------------------------------------------------------|------|-------------------|-------|
| U19487 | U19487 | 176804 | GEN-4I      | PROSTAGLANDIN E2<br>RECEPTOR, EP2<br>SUBTYPE                               | 231  | 75A>T             | S     |
| U19720 | U19720 | 600424 | GEN-I1      | Folate Transporter<br>(SLC19A1)                                            | 53   | (-43)T>C          | 5     |
| U19720 | U19720 | 600424 | GEN-I1      | Folate Transporter<br>(SLC19A1)                                            | 175  | 80G>A             | R27H  |
| U19720 | U19720 | 600424 | GEN-I1      | Folate Transporter<br>(SLC19A1)                                            | 175  | 80G>A             | R27H  |
| U19720 | U19720 | 600424 | GEN-I1      | Folate Transporter<br>(SLC19A1)                                            | 341  | 246C>G            | S     |
| U19720 | U19720 | 600424 | GEN-I1      | Folate Transporter<br>(SLC19A1)                                            | 791  | 696C>T            | S     |
| U19720 | U19720 | 600424 | GEN-I1      | Folate Transporter<br>(SLC19A1)                                            | 1067 | 972G>A            | S     |
| U19720 | U19720 | 600424 | GEN-I1      | Folate Transporter<br>(SLC19A1)                                            | 2100 | 2005*2006ins<br>G | F     |
| U19720 | U19720 | 600424 | GEN-I1      | Folate Transporter<br>(SLC19A1)                                            | 2582 | 248TT>G           | 3     |
| U19720 | U19720 | 600424 | GEN-I1      | Folate Transporter<br>(SLC19A1)                                            | 2582 | 2487T>G           | 3     |
| U19720 | U19720 | 600424 | GEN-I1      | Folate Transporter<br>(SLC19A1)                                            | 2617 | 2522C>T           | 3     |
| U19720 | U19720 | 600424 | GEN-I1      | Folate Transporter<br>(SLC19A1)                                            | 2617 | 2522C>T           | 3     |
| U19720 | U19720 | 600424 | GEN-I1      | Folate Transporter<br>(SLC19A1)                                            | 2652 | 2557T>C           | 3     |
| U19775 | U19775 | 600289 | GEN-<br>22C | Human MAP kinase Mxi2<br>(MXI2) mRNA, complete<br>cds                      | 731  | 688G>A            | D230N |
| U20157 | U20157 | 601690 | GEN-234     | Human platelet-activating<br>factor acetylhydrolase<br>mRNA, complete cds  | 1297 | 1136T>C           | V379A |
| U20350 | U20350 | 602237 | GEN-239     | Human G protein-coupled<br>receptor V28 mRNA,<br>complete cds              | 1304 | 1217T>C           | 3     |
| U20536 | U20536 | 601532 | GEN-<br>23K | Human cysteine protease<br>Mch2 isoform alpha (Mch2)<br>mRNA, complete cds | 982  | 904C>T            | 3     |
| U20536 | U20536 | 601532 | GEN-<br>23K | Human cysteine protease<br>Mch2 isoform alpha (Mch2)<br>mRNA, complete cds | 1117 | 1039G>A           | 3     |

|        |        |        |         |                                                                                                                                     |      |         |       |
|--------|--------|--------|---------|-------------------------------------------------------------------------------------------------------------------------------------|------|---------|-------|
| U20536 | U20536 | 601532 | GEN-23K | mRNA, complete cds<br>Human cysteine protease Mch2 isoform alpha (Mch2)                                                             | 1322 | 1244T>C | 3     |
| U20536 | U20536 | 601532 | GEN-23K | mRNA, complete cds<br>Human cysteine protease Mch2 isoform alpha (Mch2)                                                             | 1363 | 1285T>C | 3     |
| U21847 | U21847 | 601878 | GEN-252 | mRNA, complete cds<br>Human TGF-beta inducible early protein (TIEG)                                                                 | 986  | 900C>T  | S     |
| U21847 | U21847 | 601878 | GEN-252 | mRNA, complete cds<br>Human TGF-beta inducible early protein (TIEG)                                                                 | 1670 | 1584C>T | 3     |
| U21847 | U21847 | 601878 | GEN-252 | mRNA, complete cds<br>Human TGF-beta inducible early protein (TIEG)                                                                 | 2542 | 2456A>C | 3     |
| U23143 | U23143 | 138450 | GEN-M1Y | mRNA, complete cds<br>Human mitochondrial serine hydroxymethyltransferase gene, nuclear encoded mitochondrion protein, complete cds | 506  | 506T>G  | F169C |
| U25029 | U25029 | 138040 | GEN-82  | Glucocorticoid receptor alpha                                                                                                       | 335  | 335C>T  | 3     |
| U25029 | U25029 | 138040 | GEN-82  | Glucocorticoid receptor alpha                                                                                                       | 386  | 386T>C  | 3     |
| U25029 | U25029 | 138040 | GEN-82  | Glucocorticoid receptor alpha                                                                                                       | 1069 | 1069C>T | 3     |
| U27467 | U27467 | 601056 | GEN-2BX | Human Bcl-2 related (Bfl-1) mRNA, complete cds                                                                                      | 476  | 442T>C  | F148L |
| U27467 | U27467 | 601056 | GEN-2BX | Human Bcl-2 related (Bfl-1) mRNA, complete cds                                                                                      | 481  | 447A>G  | S     |
| U27467 | U27467 | 601056 | GEN-2BX | Human Bcl-2 related (Bfl-1) mRNA, complete cds                                                                                      | 542  | 508C>G  | L170V |
| U27467 | U27467 | 601056 | GEN-2BX | Human Bcl-2 related (Bfl-1) mRNA, complete cds                                                                                      | 578  | 544C>T  | 3     |
| U27467 | U27467 | 601056 | GEN-2BX | Human Bcl-2 related (Bfl-1) mRNA, complete cds                                                                                      | 614  | 580T>C  | 3     |
| U27467 | U27467 | 601056 | GEN-2BX | Human Bcl-2 related (Bfl-1) mRNA, complete cds                                                                                      | 616  | 582G>A  | 3     |
| CSNK1D | U29171 | 600864 | GEN-    | mRNA, complete cds<br>Human casein kinase I                                                                                         | 1612 | 1435C>A | 3     |

|        |        |        |               |                                                                                    |      |         |       |
|--------|--------|--------|---------------|------------------------------------------------------------------------------------|------|---------|-------|
| U31628 | U31628 | 601070 | 2E2<br>GEN-4J | delta mRNA, complete cds                                                           | 1250 | 1168G>T | 3     |
| U32324 | U32324 | 600939 | GEN-4K        | Interleukin 15 receptor<br>alpha chain                                             | 1266 | 1205C>A | P402Q |
| U32324 | U32324 | 600939 | GEN-4K        | interleukin 11 receptor<br>alpha chain                                             | 1513 | 1452C>T | 3     |
| U32989 | U32989 | 191070 | GEN-2JH       | interleukin 11 receptor<br>alpha chain                                             | 991  | 927G>A  | S     |
| U33017 | U33017 | 603492 | GEN-2JO       | Human tryptophan<br>oxygenase (TDO) mRNA,<br>complete cds                          | 1489 | 1356A>T | 3     |
| U33017 | U33017 | 603492 | GEN-2JO       | Human signaling<br>lymphocytic activation<br>molecule (SLAM) mRNA,<br>complete cds | 1661 | 1528C>T | 3     |
| U37448 | U37448 | 601761 | GEN-2OC       | Human signaling<br>lymphocytic activation<br>molecule (SLAM) mRNA,<br>complete cds | 736  | 693G>A  | S     |
| U37448 | U37448 | 601761 | GEN-2OC       | Human Mch3 isoform<br>alpha (Mch3) mRNA,<br>complete cds                           | 1285 | 1242T>C | 3     |
| U37448 | U37448 | 601761 | GEN-2OC       | Human Mch3 isoform<br>alpha (Mch3) mRNA,<br>complete cds                           | 1294 | 1251T>C | 3     |
| U37448 | U37448 | 601761 | GEN-2OC       | Human Mch3 isoform<br>alpha (Mch3) mRNA,<br>complete cds                           | 1580 | 1537A>T | 3     |
| U37448 | U37448 | 601761 | GEN-2OC       | Human Mch3 isoform<br>alpha (Mch3) mRNA,<br>complete cds                           | 1621 | 1578G>T | 3     |
| U37448 | U37448 | 601761 | GEN-2OC       | Human Mch3 isoform<br>alpha (Mch3) mRNA,<br>complete cds                           | 1715 | 1672G>A | 3     |
| U37448 | U37448 | 601761 | GEN-2OC       | Human Mch3 isoform<br>alpha (Mch3) mRNA,<br>complete cds                           | 1764 | 1721G>A | 3     |
| U37518 | U37518 | None   | GEN-2OG       | Human Mch3 isoform<br>alpha (Mch3) mRNA,<br>complete cds                           | 912  | 825C>T  | S     |
|        |        |        |               | Human TNF-related<br>apoptosis inducing ligand                                     |      |         |       |

|        |        |        |         |                                                                      |      |         |       |
|--------|--------|--------|---------|----------------------------------------------------------------------|------|---------|-------|
| U37518 | U37518 | None   | GEN-2OG | TRAIL mRNA, complete cds                                             | 1140 | 1053A>G | 3     |
| U37518 | U37518 | None   | GEN-2OG | Human TNF-related apoptosis inducing ligand TRAIL mRNA, complete cds | 1289 | 1202C>A | 3     |
| U37518 | U37518 | None   | GEN-2OG | Human TNF-related apoptosis inducing ligand TRAIL mRNA, complete cds | 1525 | 1438G>A | 3     |
| U37518 | U37518 | None   | GEN-2OG | Human TNF-related apoptosis inducing ligand TRAIL mRNA, complete cds | 1588 | 1501G>A | 3     |
| U37518 | U37518 | None   | GEN-2OG | Human TNF-related apoptosis inducing ligand TRAIL mRNA, complete cds | 1595 | 1508C>T | 3     |
| TAC2   | U37529 | 162320 | GEN-2OH | Substance P beta-PPT-A                                               | 644  | 499G>A  | 3     |
| TAC2   | U37529 | 162320 | GEN-2OH | Substance P beta-PPT-A                                               | 694  | 549T>C  | 3     |
| TAC2   | U37529 | 162320 | GEN-2OH | Substance P beta-PPT-A                                               | 799  | 654A>G  | 3     |
| TAC2   | U37529 | 162320 | GEN-2OH | Substance P beta-PPT-A                                               | 826  | 681C>T  | 3     |
| U39656 | U39656 | 601254 | GEN-2Q8 | Human MAP kinase kinase 6 (MKK6) mRNA, complete cds                  | 431  | 91A>C   | S     |
| U39656 | U39656 | 601254 | GEN-2Q8 | Human MAP kinase kinase 6 (MKK6) mRNA, complete cds                  | 713  | 373G>A  | V125M |
| U40038 | U40038 | 600998 | GEN-7O  | Guanine nucleotide binding protein (G protein), q polypeptide        | 825  | 783C>T  | S     |
| U40038 | U40038 | 600998 | GEN-7O  | Guanine nucleotide binding protein (G protein), q                    | 878  | 836T>C  | L279P |

|        |        |        |         |                                                               |      |         |       |
|--------|--------|--------|---------|---------------------------------------------------------------|------|---------|-------|
| U40038 | U40038 | 600998 | GEN-70  | Guanine nucleotide binding protein (G protein), q polypeptide | 1029 | 987G>A  | S     |
| U40038 | U40038 | 600998 | GEN-70  | Guanine nucleotide binding protein (G protein), q polypeptide | 1051 | 1009A>G | I337V |
| U40038 | U40038 | 600998 | GEN-70  | Guanine nucleotide binding protein (G protein), q polypeptide | 1068 | 1026T>A | S     |
| U40038 | U40038 | 600998 | GEN-70  | Guanine nucleotide binding protein (G protein), q polypeptide | 1093 | 1051T>C | S     |
| U40282 | U40282 | 602366 | GEN-2RJ | Homo sapiens integrin-linked kinase (ILK) mRNA, complete cds  | 453  | 297C>T  | S     |
| U40282 | U40282 | 602366 | GEN-2RJ | Homo sapiens integrin-linked kinase (ILK) mRNA, complete cds  | 975  | 819G>A  | S     |
| U40282 | U40282 | 602366 | GEN-2RJ | Homo sapiens integrin-linked kinase (ILK) mRNA, complete cds  | 1580 | 1424G>A | 3     |
| U40282 | U40282 | 602366 | GEN-2RJ | Homo sapiens integrin-linked kinase (ILK) mRNA, complete cds  | 1670 | 1514G>C | 3     |
| U40282 | U40282 | 602366 | GEN-2RJ | Homo sapiens integrin-linked kinase (ILK) mRNA, complete cds  | 1769 | 1613A>C | 3     |
| U40347 | U40347 | 600950 | GEN-2RK | Human serotonin N-acetyltransferase mRNA, complete cds        | 382  | 148G>A  | E50K  |
| U40583 | U40583 | 118511 | GEN-4O  | Nicotinic, Cholinergic receptor alpha 7                       | 661  | 654T>C  | S     |
| U40583 | U40583 | 118511 | GEN-4O  | Nicotinic, Cholinergic receptor alpha 7                       | 697  | 690A>G  | S     |
| U40583 | U40583 | 118511 | GEN-4O  | Nicotinic, Cholinergic receptor alpha 7                       | 940  | 933G>A  | S     |
| U40583 | U40583 | 118511 | GEN-4O  | Nicotinic, Cholinergic receptor alpha 7                       | 1276 | 1269T>C | S     |
| U40583 | U40583 | 118511 | GEN-4O  | Nicotinic, Cholinergic receptor alpha 7                       | 1790 | 1783A>T | 3     |



|        |        |        |             |                                                                                          |      |         |       |
|--------|--------|--------|-------------|------------------------------------------------------------------------------------------|------|---------|-------|
| U40583 | U40583 | 118511 | GEN-4O      | Nicotinic, Cholinergic<br>receptor alpha 7                                               | 1792 | 1785T>A | 3     |
| U43030 | U43030 | 600435 | GEN-LFI     | Human cardiostrophin-1<br>(CTF1) mRNA, complete<br>cds                                   | 1404 | 1372C>T | 3     |
| U43142 | U43142 | 601528 | GEN-<br>2UM | Human vascular<br>endothelial growth factor<br>related protein VRP<br>mRNA, complete cds | 1499 | 1128C>T | S     |
| LEPR   | U43168 | 601007 | GEN-<br>2UN | Human leptin receptor (Ob-<br>r) mRNA, complete cds                                      | 446  | 253A>G  | T85A  |
| LEPR   | U43168 | 601007 | GEN-<br>2UN | Human leptin receptor (Ob-<br>r) mRNA, complete cds                                      | 519  | 326A>G  | K109R |
| LEPR   | U43168 | 601007 | GEN-<br>2UN | Human leptin receptor (Ob-<br>r) mRNA, complete cds                                      | 861  | 668A>G  | Q223R |
| LEPR   | U43168 | 601007 | GEN-<br>2UN | Human leptin receptor (Ob-<br>r) mRNA, complete cds                                      | 1222 | 1029T>C | S     |
| LEPR   | U43168 | 601007 | GEN-<br>2UN | Human leptin receptor (Ob-<br>r) mRNA, complete cds                                      | 2161 | 1968G>C | K656N |
| LEPR   | U43168 | 601007 | GEN-<br>2UN | Human leptin receptor (Ob-<br>r) mRNA, complete cds                                      | 2174 | 1981A>C | T661P |
| LEPR   | U43168 | 601007 | GEN-<br>2UN | Human leptin receptor (Ob-<br>r) mRNA, complete cds                                      | 2764 | 2571T>G | S     |
| LEPR   | U43168 | 601007 | GEN-<br>2UN | Human leptin receptor (Ob-<br>r) mRNA, complete cds                                      | 3151 | 2958C>T | S     |
| LEPR   | U43168 | 601007 | GEN-<br>2UN | Human leptin receptor (Ob-<br>r) mRNA, complete cds                                      | 3250 | 3057G>A | S     |
| U45448 | U45448 | 600845 | GEN-4FI     | Human P2x1 receptor<br>mRNA, complete cds                                                | 1424 | 1228A>G | 3     |
| U45448 | U45448 | 600845 | GEN-4FI     | Human P2x1 receptor<br>mRNA, complete cds                                                | 1604 | 1408C>G | 3     |
| U45448 | U45448 | 600845 | GEN-4FI     | Human P2x1 receptor<br>mRNA, complete cds                                                | 1719 | 1523G>A | 3     |
| U45448 | U45448 | 600845 | GEN-4FI     | Human P2x1 receptor<br>mRNA, complete cds                                                | 1827 | 1631G>A | 3     |
| U45448 | U45448 | 600845 | GEN-4FI     | Human P2x1 receptor<br>mRNA, complete cds                                                | 2286 | 2090G>A | 3     |
| SCYA11 | U46573 | 601156 | GEN-<br>2WZ | Human eotaxin precursor<br>mRNA, complete cds                                            | 120  | 67G>A   | A23T  |
| SCYA11 | U46573 | 601156 | GEN-<br>2WZ | Human eotaxin precursor<br>mRNA, complete cds                                            | 554  | 501T>C  | 3     |

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|        |        |        |         |                                                                                 |      |         |       |
|--------|--------|--------|---------|---------------------------------------------------------------------------------|------|---------|-------|
| U47634 | U47634 | None   | GEN-2XR | Human beta-tubulin class III isotype (beta-3) mRNA, complete cds                | 1005 | 1005C>T | S     |
| U47634 | U47634 | None   | GEN-2XR | Human beta-tubulin class III isotype (beta-3) mRNA, complete cds                | 1035 | 1035C>T | S     |
| U47634 | U47634 | None   | GEN-2XR | Human beta-tubulin class III isotype (beta-3) mRNA, complete cds                | 1431 | 1431T>C | 3     |
| U47634 | U47634 | None   | GEN-2XR | Human beta-tubulin class III isotype (beta-3) mRNA, complete cds                | 1502 | 1502G>A | 3     |
| U49516 | U49516 | 312861 | GEN-1Q  | Serotonin 5-HT receptors 5-HT2C                                                 | 2915 | 2187A>C | 3     |
| U49516 | U49516 | 312861 | GEN-1Q  | Serotonin 5-HT receptors 5-HT2C                                                 | 2947 | 2219A>G | 3     |
| U50040 | U50040 | 601582 | GEN-2ZR | Human signaling inositol polyphosphate 5 phosphatase SIP-110 mRNA, complete cds | 196  | 180A>G  | S     |
| U50040 | U50040 | 601582 | GEN-2ZR | Human signaling inositol polyphosphate 5 phosphatase SIP-110 mRNA, complete cds | 418  | 402C>G  | S     |
| U50040 | U50040 | 601582 | GEN-2ZR | Human signaling inositol polyphosphate 5 phosphatase SIP-110 mRNA, complete cds | 2613 | 2597C>A | P866H |
| U50040 | U50040 | 601582 | GEN-2ZR | Human signaling inositol polyphosphate 5 phosphatase SIP-110 mRNA, complete cds | 2638 | 2622G>A | S     |
| U50040 | U50040 | 601582 | GEN-2ZR | Human signaling inositol polyphosphate 5 phosphatase SIP-110 mRNA, complete cds | 2882 | 2866C>T | H956Y |
| U50040 | U50040 | 601582 | GEN-2ZR | Human signaling inositol polyphosphate 5 phosphatase SIP-110 mRNA, complete cds | 3193 | 3177C>T | 3     |
| U50040 | U50040 | 601582 | GEN-2ZR | Human signaling inositol polyphosphate 5 phosphatase SIP-110 mRNA, complete cds | 3222 | 3206C>T | 3     |

|        |        |        |        |             |                                                                                                                                   |      |         |       |
|--------|--------|--------|--------|-------------|-----------------------------------------------------------------------------------------------------------------------------------|------|---------|-------|
| 2ZR    |        |        |        |             | polyphosphate 5<br>phosphatase SIP-110<br>mRNA, complete cds                                                                      |      |         |       |
| U50040 | IRF4   | U50040 | 601582 | GEN-<br>2ZR | Human signaling inositol<br>polyphosphate 5<br>phosphatase SIP-110<br>mRNA, complete cds                                          | 3863 | 3847G>A | 3     |
|        | IRF4   | U52682 | 601900 | GEN-<br>33X | Human lymphocyte specific<br>interferon regulatory<br>factor/interferon regulatory<br>factor 4 (LSIRF/IRF4)<br>mRNA, complete cds | 4296 | 4297G>A | 3     |
|        | IRF4   | U52682 | 601900 | GEN-<br>33X | Human lymphocyte specific<br>interferon regulatory<br>factor/interferon regulatory<br>factor 4 (LSIRF/IRF4)<br>mRNA, complete cds | 4680 | 4681T>G | 3     |
|        | IRF4   | U52682 | 601900 | GEN-<br>33X | Human lymphocyte specific<br>interferon regulatory<br>factor/interferon regulatory<br>factor 4 (LSIRF/IRF4)<br>mRNA, complete cds | 4732 | 4733T>G | 3     |
|        | IRF4   | U52682 | 601900 | GEN-<br>33X | Human lymphocyte specific<br>interferon regulatory<br>factor/interferon regulatory<br>factor 4 (LSIRF/IRF4)<br>mRNA, complete cds | 4942 | 4943A>G | 3     |
|        | IRF4   | U52682 | 601900 | GEN-<br>33X | Human lymphocyte specific<br>interferon regulatory<br>factor/interferon regulatory<br>factor 4 (LSIRF/IRF4)<br>mRNA, complete cds | 5079 | 5080T>C | 3     |
|        | U55206 | U55206 | None   | GEN-<br>35Z | Homo sapiens human<br>gamma-glutamyl hydrolase<br>(hGH) mRNA, complete<br>cds                                                     | 75   | 16T>C   | C6R   |
|        | U55206 | U55206 | None   | GEN-<br>35Z | Homo sapiens human<br>gamma-glutamyl hydrolase<br>(hGH) mRNA, complete<br>cds                                                     | 150  | 91G>A   | A31T  |
|        | U55206 | U55206 | None   | GEN-        | Homo sapiens human<br>cds                                                                                                         | 511  | 452C>T  | T151I |

|        |        |        |         |                                                                                              |      |         |       |
|--------|--------|--------|---------|----------------------------------------------------------------------------------------------|------|---------|-------|
| U55206 | U55206 | None   | GEN-35Z | 35Z gamma-glutamyl hydrolase (hGH) mRNA, complete cds                                        | 1161 | 1102A>G | 3     |
| U56390 | U56390 | 602234 | GEN-36X | Homo sapiens human gamma-glutamyl hydrolase (hGH) mRNA, complete cds                         | 411  | 408C>T  | S     |
| U58196 | U58196 | 147685 | GEN-67  | Human cysteine protease ICE-LAP6 mRNA, complete cds                                          | 2711 | 2514A>G | 3     |
| U59863 | U59863 | None   | GEN-3A7 | INTERLEUKIN ENHANCER-BINDING FACTOR Human TRAF-interacting protein I-TRAF mRNA, complete cds | 367  | 209A>G  | D70G  |
| U59863 | U59863 | None   | GEN-3A7 | Human TRAF-interacting protein I-TRAF mRNA, complete cds                                     | 1863 | 1705A>T | 3     |
| U59863 | U59863 | None   | GEN-3A7 | Human TRAF-interacting protein I-TRAF mRNA, complete cds                                     | 2046 | 1888G>A | 3     |
| U60519 | U60519 | 601762 | GEN-3AZ | Human apoptotic cysteine protease Mch4 (Mch4) mRNA, complete cds                             | 304  | 157G>A  | E53K  |
| U60519 | U60519 | 601762 | GEN-3AZ | Human apoptotic cysteine protease Mch4 (Mch4) mRNA, complete cds                             | 324  | 177A>G  | S     |
| U60800 | U60800 | None   | GEN-3BC | Human semaphorin (CD100) mRNA, complete cds                                                  | 779  | 692T>G  | V231G |
| U61849 | U61849 | 602367 | GEN-3C0 | Human neuronal pentraxin 1 (NPTX1) mRNA, complete cds                                        | 4963 | 4825T>C | 3     |
| CHRNA2 | U62431 | 118502 | GEN-4EN | Nicotinic, Cholinergic receptor alpha 2                                                      | 2296 | 1742C>G | 3     |
| CHRNA2 | U62431 | 118502 | GEN-4EN | Nicotinic, Cholinergic receptor alpha 2                                                      | 2387 | 1833C>T | 3     |
| CHRNA2 | U62431 | 118502 | GEN-4EN | Nicotinic, Cholinergic receptor alpha 2                                                      | 2504 | 1950G>T | 3     |
| CHRNA2 | U62431 | 118502 | GEN-4EN | Nicotinic, Cholinergic receptor alpha 2                                                      | 2538 | 1984G>A | 3     |

|        |        |        |               |                                                           |      |         |       |
|--------|--------|--------|---------------|-----------------------------------------------------------|------|---------|-------|
| U62433 | U62433 | 118504 | 4EN<br>GEN-4P | receptor alpha 2<br>Nicotinic, Cholinergic                | 870  | 639C>T  | S     |
| U62433 | U62433 | 118504 | GEN-4P        | receptor alpha 4<br>Nicotinic, Cholinergic                | 870  | 639C>T  | S     |
| U62433 | U62433 | 118504 | GEN-4P        | receptor alpha 4<br>Nicotinic, Cholinergic                | 909  | 678C>T  | S     |
| U62433 | U62433 | 118504 | GEN-4P        | receptor alpha 4<br>Nicotinic, Cholinergic                | 909  | 678C>T  | S     |
| U62433 | U62433 | 118504 | GEN-4P        | receptor alpha 4<br>Nicotinic, Cholinergic                | 1440 | 1209T>G | S     |
| U62433 | U62433 | 118504 | GEN-4P        | receptor alpha 4<br>Nicotinic, Cholinergic                | 1440 | 1209T>G | S     |
| U62433 | U62433 | 118504 | GEN-4P        | receptor alpha 4<br>Nicotinic, Cholinergic                | 1458 | 1227C>T | S     |
| U62433 | U62433 | 118504 | GEN-4P        | receptor alpha 4<br>Nicotinic, Cholinergic                | 1584 | 1353G>A | S     |
| U62433 | U62433 | 118504 | GEN-4P        | receptor alpha 4<br>Nicotinic, Cholinergic                | 1781 | 1550C>T | S517L |
| U62433 | U62433 | 118504 | GEN-4P        | receptor alpha 4<br>Nicotinic, Cholinergic                | 1860 | 1629C>T | S     |
| U62433 | U62433 | 118504 | GEN-4P        | receptor alpha 4<br>Nicotinic, Cholinergic                | 1860 | 1629C>T | S     |
| U62433 | U62433 | 118504 | GEN-4P        | receptor alpha 4<br>Nicotinic, Cholinergic                | 1890 | 1659G>A | S     |
| U62433 | U62433 | 118504 | GEN-4P        | receptor alpha 4<br>Nicotinic, Cholinergic                | 1890 | 1659G>A | S     |
| U70321 | U70321 | None   | GEN-<br>3K9   | Human herpesvirus entry<br>mediator mRNA, complete<br>cds | 343  | 50G>A   | R17K  |
| U70321 | U70321 | None   | GEN-<br>3K9   | Human herpesvirus entry<br>mediator mRNA, complete<br>cds | 1014 | 721G>A  | V241I |
| U70321 | U70321 | None   | GEN-<br>3K9   | Human herpesvirus entry<br>mediator mRNA, complete<br>cds | 1218 | 925A>G  | 3     |
| U70321 | U70321 | None   | GEN-<br>3K9   | Human herpesvirus entry<br>mediator mRNA, complete<br>cds | 1249 | 956C>T  | 3     |
| U70321 | U70321 | None   | GEN-<br>3K9   | Human herpesvirus entry<br>mediator mRNA, complete<br>cds | 1453 | 1160G>A | 3     |

|        |        |        |         |                                                                                        |      |         |       |
|--------|--------|--------|---------|----------------------------------------------------------------------------------------|------|---------|-------|
| U70451 | U70451 | 602170 | GEN-3KB | cds<br>Human myleoid differentiation primary response protein MyD88 mRNA, complete cds | 2167 | 2135A>G | 3     |
| U70451 | U70451 | 602170 | GEN-3KB | Human myleoid differentiation primary response protein MyD88 mRNA, complete cds        | 2516 | 2484A>G | 3     |
| U71321 | U71321 | 602623 | GEN-2TW | Human FK506-binding protein FKBP51 mRNA, complete cds                                  | 1248 | 1095C>T | S     |
| U71321 | U71321 | 602623 | GEN-2TW | Human FK506-binding protein FKBP51 mRNA, complete cds                                  | 1425 | 1272G>A | S     |
| U73338 | U73338 | 156570 | GEN-69  | Methionine Synthase                                                                    | 1158 | 764G>A  | C255Y |
| U73338 | U73338 | 156570 | GEN-69  | Methionine Synthase                                                                    | 5095 | 4701G>A | 3     |
| U73338 | U73338 | 156570 | GEN-69  | Methionine Synthase                                                                    | 6750 | 6356G>A | 3     |
| U75283 | U75283 | None   | GEN-3NV | Human sigma receptor mRNA, complete cds                                                | 251  | 204G>A  | S     |
| U75283 | U75283 | None   | GEN-3NV | Human sigma receptor mRNA, complete cds                                                | 1625 | 1578A>C | 3     |
| U78294 | U78294 | 603697 | GEN-3QZ | Homo sapiens 15S-lipoxygenase mRNA, complete cds                                       | 2449 | 2378A>G | 3     |
| U81375 | U81375 | 602193 | GEN-3VO | Human placental equilibrative nucleoside transporter 1 (hENT1) mRNA, complete cds      | 1989 | 1811G>A | 3     |
| U81375 | U81375 | 602193 | GEN-3VO | Human placental equilibrative nucleoside transporter 1 (hENT1) mRNA, complete cds      | 1996 | 1818C>T | 3     |
| U81375 | U81375 | 602193 | GEN-3VO | Human placental equilibrative nucleoside transporter 1 (hENT1) mRNA, complete cds      | 2045 | 1867T>C | 3     |
| U84487 | U84487 | 601880 | GEN-3ZJ | Human CX3C chemokine precursor, mRNA, alternatively spliced, complete cds              | 3015 | 2936T>C | 3     |

|        |        |        |         |                                                                           |      |          |       |
|--------|--------|--------|---------|---------------------------------------------------------------------------|------|----------|-------|
| U84487 | U84487 | 601880 | GEN-3ZJ | Human CX3C chemokine precursor, mRNA, alternatively spliced, complete cds | 3058 | 2979T>C  | 3     |
| U86358 | U86358 | 602565 | GEN-LR6 | Human chemokine (TECK) mRNA, complete cds                                 | 378  | 378A>G   | S     |
| CD39   | U87967 | 601752 | GEN-44L | Human ATP diphosphohydrolase mRNA, complete cds                           | 1233 | 1203C>T  | S     |
| V00537 | V00537 | 147578 | GEN-U1  | Interferon alpha 13                                                       | 40   | (-17)T>C | 5     |
| V00537 | V00537 | 147578 | GEN-U1  | Interferon alpha 13                                                       | 55   | (-2)C>T  | 5     |
| V00537 | V00537 | 147578 | GEN-U1  | Interferon alpha 13                                                       | 466  | 410C>T   | A137V |
| V00537 | V00537 | 147578 | GEN-U1  | Interferon alpha 13                                                       | 808  | 752G>A   | 3     |
| IFNA14 | V00542 | 147579 | GEN-TT  | Interferon alpha 14                                                       | 47   | (-10)G>A | 5     |
| IFNA14 | V00542 | 147579 | GEN-TT  | Interferon alpha 14                                                       | 50   | (-7)A>G  | 5     |
| IFNA14 | V00542 | 147579 | GEN-TT  | Interferon alpha 14                                                       | 579  | 523T>C   | F175L |
| IFNA14 | V00542 | 147579 | GEN-TT  | Interferon alpha 14                                                       | 630  | 574C>G   | 3     |
| IFNA14 | V00542 | 147579 | GEN-TT  | Interferon alpha 14                                                       | 740  | 684C>T   | 3     |
| IFNA14 | V00542 | 147579 | GEN-TT  | Interferon alpha 14                                                       | 760  | 704T>A   | 3     |
| IFNA14 | V00542 | 147579 | GEN-TT  | Interferon alpha 14                                                       | 771  | 715G>A   | 3     |
| IFNA14 | V00542 | 147579 | GEN-TT  | Interferon alpha 14                                                       | 775  | 719T>A   | 3     |
| IFNA14 | V00542 | 147579 | GEN-TT  | Interferon alpha 14                                                       | 812  | 756T>G   | 3     |
| IFNA14 | V00542 | 147579 | GEN-TT  | Interferon alpha 14                                                       | 898  | 842A>T   | 3     |
| IFNA14 | V00542 | 147579 | GEN-TT  | Interferon alpha 14                                                       | 921  | 865G>A   | 3     |
| IFNB1  | V00546 | 147640 | GEN-TV  | Messenger RNA for human fibroblast interferon                             | 474  | 410T>G   | L137R |
| V00548 | V00548 | 147562 | GEN-P2  | Human messenger RNA for leukocyte (alpha-2) interferon                    | 119  | 119G>A   | R40K  |
| IFNA10 | V00551 | 147577 | GEN-TS  | Interferon alpha 7                                                        | 462  | 416C>T   | S139F |
| IFNA10 | V00551 | 147577 | GEN-TS  | Interferon alpha 7                                                        | 510  | 464T>C   | I155T |
| IFNA10 | V00551 | 147577 | GEN-TS  | Interferon alpha 7                                                        | 516  | 470G>A   | R157K |
| IFNA10 | V00551 | 147577 | GEN-TS  | Interferon alpha 7                                                        | 712  | 666G>C   | 3     |
| IFNA10 | V00551 | 147577 | GEN-TS  | Interferon alpha 7                                                        | 716  | 670C>T   | 3     |
| V00567 | V00567 | 109700 | GEN-P3  | Human messenger RNA fragment for the beta-2 microglobulin                 | 303  | 303C>A   | S     |
| HLA-   | X00033 | 146880 | GEN-T0  | Human RNA sequence of                                                     | 41   | 22A>C    | M8L   |

[illegible]



|          |        |        |        |                                                                                                                                  |     |        |      |
|----------|--------|--------|--------|----------------------------------------------------------------------------------------------------------------------------------|-----|--------|------|
| HLA-DQA1 | X00033 | 146880 | GEN-T0 | Human RNA sequence of the human DS glycoprotein alpha subunit from the HLA-D region of the major histocompatibility complex(MHC) | 243 | 224A>G | H75R |
| HLA-DQA1 | X00033 | 146880 | GEN-T0 | Human RNA sequence of the human DS glycoprotein alpha subunit from the HLA-D region of the major histocompatibility complex(MHC) | 248 | 229C>T | L77F |
| HLA-DQA1 | X00033 | 146880 | GEN-T0 | Human RNA sequence of the human DS glycoprotein alpha subunit from the HLA-D region of the major histocompatibility complex(MHC) | 298 | 279T>C | S    |
| HLA-DQA1 | X00033 | 146880 | GEN-T0 | Human RNA sequence of the human DS glycoprotein alpha subunit from the HLA-D region of the major histocompatibility complex(MHC) | 311 | 292C>G | L98V |
| HLA-DQA1 | X00033 | 146880 | GEN-T0 | Human RNA sequence of the human DS glycoprotein alpha subunit from the HLA-D region of the major histocompatibility complex(MHC) | 334 | 315C>T | S    |
| HLA-DQA1 | X00033 | 146880 | GEN-T0 | Human RNA sequence of the human DS glycoprotein alpha subunit from the HLA-D region of the major histocompatibility complex(MHC) | 388 | 369A>G | S    |
| HLA-DQA1 | X00033 | 146880 | GEN-T0 | Human RNA sequence of the human DS glycoprotein alpha subunit from the HLA-D region of the major histocompatibility complex(MHC) | 559 | 540T>G | S    |

|          |        |        |        |                                                                                                                                  |     |        |       |
|----------|--------|--------|--------|----------------------------------------------------------------------------------------------------------------------------------|-----|--------|-------|
| HLA-DQA1 | X00033 | 146880 | GEN-T0 | Human RNA sequence of the human DS glycoprotein alpha subunit from the HLA-D region of the major histocompatibility complex(MHC) | 564 | 545C>A | A182D |
| HLA-DQA1 | X00033 | 146880 | GEN-T0 | Human RNA sequence of the human DS glycoprotein alpha subunit from the HLA-D region of the major histocompatibility complex(MHC) | 607 | 588T>C | S     |
| HLA-DQA1 | X00033 | 146880 | GEN-T0 | Human RNA sequence of the human DS glycoprotein alpha subunit from the HLA-D region of the major histocompatibility complex(MHC) | 644 | 625G>A | A209T |
| HLA-DQA1 | X00033 | 146880 | GEN-T0 | Human RNA sequence of the human DS glycoprotein alpha subunit from the HLA-D region of the major histocompatibility complex(MHC) | 646 | 627A>C | S     |
| HLA-DQA1 | X00033 | 146880 | GEN-T0 | Human RNA sequence of the human DS glycoprotein alpha subunit from the HLA-D region of the major histocompatibility complex(MHC) | 679 | 660T>C | S     |
| HLA-DQA1 | X00033 | 146880 | GEN-T0 | Human RNA sequence of the human DS glycoprotein alpha subunit from the HLA-D region of the major histocompatibility complex(MHC) | 688 | 669G>A | S     |
| HLA-DQA1 | X00033 | 146880 | GEN-T0 | Human RNA sequence of the human DS glycoprotein alpha subunit from the HLA-D region of the major histocompatibility complex(MHC) | 704 | 685G>A | V229M |

|          |        |        |        |                                                                                                                                  |      |         |       |
|----------|--------|--------|--------|----------------------------------------------------------------------------------------------------------------------------------|------|---------|-------|
| HLA-DQA1 | X00033 | 146880 | GEN-T0 | Human RNA sequence of the human DS glycoprotein alpha subunit from the HLA-D region of the major histocompatibility complex(MHC) | 721  | 702G>C  | S     |
| HLA-DQA1 | X00033 | 146880 | GEN-T0 | Human RNA sequence of the human DS glycoprotein alpha subunit from the HLA-D region of the major histocompatibility complex(MHC) | 724  | 705C>T  | S     |
| HLA-DQA1 | X00033 | 146880 | GEN-T0 | Human RNA sequence of the human DS glycoprotein alpha subunit from the HLA-D region of the major histocompatibility complex(MHC) | 730  | 711G>C  | L237F |
| HLA-DQA1 | X00033 | 146880 | GEN-T0 | Human RNA sequence of the human DS glycoprotein alpha subunit from the HLA-D region of the major histocompatibility complex(MHC) | 800  | 781A>G  | 3     |
| X00497   | X00497 | 142790 | GEN-TN | Human mRNA for HLA-DR antigens associated invariant chain (p33)                                                                  | 805  | 750A>G  | 3     |
| X00497   | X00497 | 142790 | GEN-TN | Human mRNA for HLA-DR antigens associated invariant chain (p33)                                                                  | 881  | 826A>G  | 3     |
| X00497   | X00497 | 142790 | GEN-TN | Human mRNA for HLA-DR antigens associated invariant chain (p33)                                                                  | 1144 | 1089C>G | 3     |
| HLA-DPB1 | X00532 | 142858 | GEN-U2 | Human mRNA for SB beta-chain (clone pII-beta-7)                                                                                  | 13   | 13T>A   | S5T   |
| HLA-DPB1 | X00532 | 142858 | GEN-U2 | Human mRNA for SB beta-chain (clone pII-beta-7)                                                                                  | 91   | 91T>A   | S31T  |
| HLA-DPB1 | X00532 | 142858 | GEN-U2 | Human mRNA for SB beta-chain (clone pII-beta-7)                                                                                  | 94   | 94C>T   | R32C  |

|          |        |        |        |                                                                |      |         |       |
|----------|--------|--------|--------|----------------------------------------------------------------|------|---------|-------|
| HLA-DPB1 | X00532 | 142858 | GEN-U2 | Human mRNA for SB beta-chain (clone pII-beta-7)                | 151  | 151C>A  | L51M  |
| HLA-DPB1 | X00532 | 142858 | GEN-U2 | Human mRNA for SB beta-chain (clone pII-beta-7)                | 154  | 154C>A  | S     |
| HLA-DPB1 | X00532 | 142858 | GEN-U2 | Human mRNA for SB beta-chain (clone pII-beta-7)                | 158  | 158G>C  | S53T  |
| HLA-DPB1 | X00532 | 142858 | GEN-U2 | Human mRNA for SB beta-chain (clone pII-beta-7)                | 213  | 213G>A  | S     |
| HLA-DPB1 | X00532 | 142858 | GEN-U2 | Human mRNA for SB beta-chain (clone pII-beta-7)                | 281  | 281C>T  | T94M  |
| HLA-DPB1 | X00532 | 142858 | GEN-U2 | Human mRNA for SB beta-chain (clone pII-beta-7)                | 306  | 306C>T  | S     |
| HLA-DPB1 | X00532 | 142858 | GEN-U2 | Human mRNA for SB beta-chain (clone pII-beta-7)                | 341  | 341A>G  | Q114R |
| HLA-DPB1 | X00532 | 142858 | GEN-U2 | Human mRNA for SB beta-chain (clone pII-beta-7)                | 353  | 353G>A  | R118Q |
| HLA-DPB1 | X00532 | 142858 | GEN-U2 | Human mRNA for SB beta-chain (clone pII-beta-7)                | 488  | 488C>T  | T163M |
| HLA-DPB1 | X00532 | 142858 | GEN-U2 | Human mRNA for SB beta-chain (clone pII-beta-7)                | 496  | 496T>C  | S166P |
| HLA-DPB1 | X00532 | 142858 | GEN-U2 | Human mRNA for SB beta-chain (clone pII-beta-7)                | 524  | 524C>T  | T175I |
| HLA-DPB1 | X00532 | 142858 | GEN-U2 | Human mRNA for SB beta-chain (clone pII-beta-7)                | 568  | 568A>G  | R190G |
| HLA-DPB1 | X00532 | 142858 | GEN-U2 | Human mRNA for SB beta-chain (clone pII-beta-7)                | 600  | 600G>A  | S     |
| HLA-DPB1 | X00532 | 142858 | GEN-U2 | Human mRNA for SB beta-chain (clone pII-beta-7)                | 708  | 708C>G  | F     |
| HLA-DPB1 | X00532 | 142858 | GEN-U2 | Human mRNA for SB beta-chain (clone pII-beta-7)                | 761  | 761G>A  | 3     |
| HLA-DPB1 | X00532 | 142858 | GEN-U2 | Human mRNA for SB beta-chain (clone pII-beta-7)                | 840  | 840G>A  | 3     |
| EGFR     | X00663 | 131550 | GEN-U4 | Human mRNA fragment for epidermal growth factor (EGF) receptor | 1136 | 1136G>A | R379K |
| EGFR     | X00663 | 131550 | GEN-U4 | Human mRNA fragment for epidermal growth factor (EGF) receptor | 1935 | 1935A>G | S     |
| EGFR     | X00663 | 131550 | GEN-U4 | Human mRNA fragment for epidermal growth factor (EGF) receptor | 2283 | 2283C>T | S     |

|        |        |        |         |                                                                   |      |          |       |
|--------|--------|--------|---------|-------------------------------------------------------------------|------|----------|-------|
| X00734 | X00734 | None   | GEN-MST | Human beta-tubulin gene (5-beta) with ten Alu family members      | 1059 | 1059G>T  | S     |
| X00737 | X00737 | 164050 | GEN-P8  | Human mRNA for purine nucleoside phosphorylase (PNP; EC 2.4.2.1)  | 59   | (-51)T>G | 5     |
| X00737 | X00737 | 164050 | GEN-P8  | Human mRNA for purine nucleoside phosphorylase (PNP; EC 2.4.2.1)  | 169  | 60T>C    | S     |
| X00737 | X00737 | 164050 | GEN-P8  | Human mRNA for purine nucleoside phosphorylase (PNP; EC 2.4.2.1)  | 260  | 151A>G   | S51G  |
| X00737 | X00737 | 164050 | GEN-P8  | Human mRNA for purine nucleoside phosphorylase (PNP; EC 2.4.2.1)  | 280  | 171T>C   | S     |
| X00737 | X00737 | 164050 | GEN-P8  | Human mRNA for purine nucleoside phosphorylase (PNP; EC 2.4.2.1)  | 1254 | 1145G>A  | 3     |
| X01394 | X01394 | 191160 | GEN-4Y  | Tumor necrosis factor                                             | 125  | (-28)C>T | 5     |
| X01586 | X01586 | 147680 | GEN-PC  | Interleukin 2                                                     | 332  | 225T>G   | H75Q  |
| X01586 | X01586 | 147680 | GEN-PC  | Interleukin 2                                                     | 563  | 456G>A   | S     |
| X02317 | X02317 | 147450 | GEN-KM  | Superoxide dismutase 1 (Cu/Zn)                                    | 614  | 550A>C   | 3     |
| X02469 | X02469 | 191170 | GEN-PF  | Human mRNA for p53 cellular tumor antigen                         | 350  | 215C>G   | P72R  |
| X02469 | X02469 | 191170 | GEN-PF  | Human mRNA for p53 cellular tumor antigen                         | 953  | 818G>A   | R273H |
| X02492 | X02492 | 147572 | GEN-1T  | Interferon alpha inducible protein                                | 415  | 346C>G   | R116G |
| X02492 | X02492 | 147572 | GEN-1T  | Interferon alpha inducible protein                                | 417  | 348G>C   | S     |
| X02598 | X02598 | 305370 | GEN-X6  | Human mRNA for EPA glycoprotein (erythroid-potentiating activity) | 64   | 23C>T    | A8V   |
| X02598 | X02598 | 305370 | GEN-X6  | Human mRNA for EPA glycoprotein (erythroid-potentiating activity) | 108  | 67C>G    | P23A  |
| X02598 | X02598 | 305370 | GEN-X6  | Human mRNA for EPA glycoprotein (erythroid-potentiating activity) | 298  | 257C>A   | T86N  |
| X02598 | X02598 | 305370 | GEN-X6  | Human mRNA for EPA glycoprotein (erythroid-potentiating activity) | 413  | 372T>C   | S     |

|         |        |        |        |                                                                  |      |          |       |
|---------|--------|--------|--------|------------------------------------------------------------------|------|----------|-------|
| X02812  | X02812 | 190180 | GEN-XR | glycoprotein (erythroid-<br>potentiating activity)               | 870  | 29C>T    | P10L  |
| X02812  | X02812 | 190180 | GEN-XR | Human mRNA for<br>transforming growth factor-<br>beta (TGF-beta) | 979  | 138C>G   | I46M  |
| X02812  | X02812 | 190180 | GEN-XR | Human mRNA for<br>transforming growth factor-<br>beta (TGF-beta) | 1632 | 791C>T   | T264I |
| X02812  | X02812 | 190180 | GEN-XR | Human mRNA for<br>transforming growth factor-<br>beta (TGF-beta) | 1807 | 986C>T   | S     |
| X02812  | X02812 | 190180 | GEN-XR | Human mRNA for<br>transforming growth factor-<br>beta (TGF-beta) | 1930 | 1089G>A  | S     |
| X02812  | X02812 | 190180 | GEN-XR | Human mRNA for<br>transforming growth factor-<br>beta (TGF-beta) | 1942 | 1101C>T  | S     |
| X02812  | X02812 | 190180 | GEN-XR | Human mRNA for<br>transforming growth factor-<br>beta (TGF-beta) | 2013 | 1172G>A  | S391N |
| HLA-DOB | X03066 | 600629 | GEN-ZG | Human mRNA for HLA-D<br>class II antigen DO beta<br>chain        | 32   | (-25)G>A | 5     |
| HLA-DOB | X03066 | 600629 | GEN-ZG | Human mRNA for HLA-D<br>class II antigen DO beta<br>chain        | 1147 | 1091C>T  | 3     |
| HLA-DOB | X03066 | 600629 | GEN-ZG | Human mRNA for HLA-D<br>class II antigen DO beta<br>chain        | 1299 | 1243A>G  | 3     |
| X03068  | X03068 | 142857 | GEN-ZH | Human mRNA for HLA-D<br>class II antigen DQw1.1<br>beta chain    | 79   | (-3)A>G  | 5     |
| X03068  | X03068 | 142857 | GEN-ZH | Human mRNA for HLA-D<br>class II antigen DQw1.1<br>beta chain    | 97   | 16T>G    | S6A   |
| X03068  | X03068 | 142857 | GEN-ZH | Human mRNA for HLA-D<br>class II antigen DQw1.1<br>beta chain    | 203  | 122A>T   | Y41F  |

|        |        |        |        |                                                               |     |        |       |
|--------|--------|--------|--------|---------------------------------------------------------------|-----|--------|-------|
| X03068 | X03068 | 142857 | GEN-ZH | Human mRNA for HLA-D<br>class II antigen DQw1.1<br>beta chain | 318 | 237C>T | S     |
| X03068 | X03068 | 142857 | GEN-ZH | Human mRNA for HLA-D<br>class II antigen DQw1.1<br>beta chain | 408 | 327G>A | S     |
| X03068 | X03068 | 142857 | GEN-ZH | Human mRNA for HLA-D<br>class II antigen DQw1.1<br>beta chain | 523 | 442A>G | I148V |
| X03068 | X03068 | 142857 | GEN-ZH | Human mRNA for HLA-D<br>class II antigen DQw1.1<br>beta chain | 550 | 469A>G | S157G |
| X03068 | X03068 | 142857 | GEN-ZH | Human mRNA for HLA-D<br>class II antigen DQw1.1<br>beta chain | 566 | 485G>A | R162Q |
| X03068 | X03068 | 142857 | GEN-ZH | Human mRNA for HLA-D<br>class II antigen DQw1.1<br>beta chain | 597 | 516C>T | S     |
| X03068 | X03068 | 142857 | GEN-ZH | Human mRNA for HLA-D<br>class II antigen DQw1.1<br>beta chain | 618 | 537C>T | S     |
| X03068 | X03068 | 142857 | GEN-ZH | Human mRNA for HLA-D<br>class II antigen DQw1.1<br>beta chain | 627 | 546C>T | S     |
| X03068 | X03068 | 142857 | GEN-ZH | Human mRNA for HLA-D<br>class II antigen DQw1.1<br>beta chain | 639 | 558C>T | S     |
| X03068 | X03068 | 142857 | GEN-ZH | Human mRNA for HLA-D<br>class II antigen DQw1.1<br>beta chain | 677 | 596G>A | R199H |
| X03068 | X03068 | 142857 | GEN-ZH | Human mRNA for HLA-D<br>class II antigen DQw1.1<br>beta chain | 684 | 603T>C | S     |
| X03068 | X03068 | 142857 | GEN-ZH | Human mRNA for HLA-D<br>class II antigen DQw1.1<br>beta chain | 767 | 686G>A | S229N |
| X03068 | X03068 | 142857 | GEN-ZH | Human mRNA for HLA-D<br>class II antigen DQw1.1<br>beta chain | 784 | 703G>A | V235I |
| X03068 | X03068 | 142857 | GEN-ZH | Human mRNA for HLA-D<br>class II antigen DQw1.1<br>beta chain | 816 | 735T>C | S     |

|        |        |        |        |                                                               |      |         |       |
|--------|--------|--------|--------|---------------------------------------------------------------|------|---------|-------|
| X03068 | X03068 | 142857 | GEN-ZH | Human mRNA for HLA-D<br>class II antigen DQw1.1<br>beta chain | 822  | 741T>G  | S     |
| X03068 | X03068 | 142857 | GEN-ZH | Human mRNA for HLA-D<br>class II antigen DQw1.1<br>beta chain | 848  | 767G>A  | R256Q |
| X03068 | X03068 | 142857 | GEN-ZH | Human mRNA for HLA-D<br>class II antigen DQw1.1<br>beta chain | 879  | 798G>A  | 3     |
| X03068 | X03068 | 142857 | GEN-ZH | Human mRNA for HLA-D<br>class II antigen DQw1.1<br>beta chain | 889  | 808A>G  | 3     |
| X03068 | X03068 | 142857 | GEN-ZH | Human mRNA for HLA-D<br>class II antigen DQw1.1<br>beta chain | 892  | 811C>T  | 3     |
| X03068 | X03068 | 142857 | GEN-ZH | Human mRNA for HLA-D<br>class II antigen DQw1.1<br>beta chain | 924  | 843C>G  | 3     |
| X03068 | X03068 | 142857 | GEN-ZH | Human mRNA for HLA-D<br>class II antigen DQw1.1<br>beta chain | 998  | 917A>G  | 3     |
| X03068 | X03068 | 142857 | GEN-ZH | Human mRNA for HLA-D<br>class II antigen DQw1.1<br>beta chain | 1073 | 992A>T  | 3     |
| X03068 | X03068 | 142857 | GEN-ZH | Human mRNA for HLA-D<br>class II antigen DQw1.1<br>beta chain | 1082 | 1001A>G | 3     |
| X03068 | X03068 | 142857 | GEN-ZH | Human mRNA for HLA-D<br>class II antigen DQw1.1<br>beta chain | 1095 | 1014C>T | 3     |
| X03068 | X03068 | 142857 | GEN-ZH | Human mRNA for HLA-D<br>class II antigen DQw1.1<br>beta chain | 1107 | 1026C>T | 3     |
| X03068 | X03068 | 142857 | GEN-ZH | Human mRNA for HLA-D<br>class II antigen DQw1.1<br>beta chain | 1117 | 1036A>T | 3     |
| X03068 | X03068 | 142857 | GEN-ZH | Human mRNA for HLA-D<br>class II antigen DQw1.1<br>beta chain | 1128 | 1047G>A | 3     |
| X03068 | X03068 | 142857 | GEN-ZH | Human mRNA for HLA-D<br>class II antigen DQw1.1<br>beta chain | 1133 | 1052C>T | 3     |



|        |        |        |        |                                                   |      |         |       |
|--------|--------|--------|--------|---------------------------------------------------|------|---------|-------|
| X03068 | X03068 | 142857 | GEN-ZH | class II antigen DQw1.1<br>beta chain             | 1180 | 1099C>T | 3     |
|        |        |        |        | Human mRNA for HLA-D<br>class II antigen DQw1.1   |      |         |       |
| X03069 | X03069 | 142857 | GEN-PI | class II antigen DQw1.1<br>beta chain             | 99   | 37A>G   | T13A  |
|        |        |        |        | Human mRNA for HLA-D<br>class II antigen DR1 beta |      |         |       |
| X03069 | X03069 | 142857 | GEN-PI | chain                                             | 104  | 42G>T   | S     |
|        |        |        |        | Human mRNA for HLA-D<br>class II antigen DR1 beta |      |         |       |
| X03069 | X03069 | 142857 | GEN-PI | chain                                             | 348  | 286C>A  | L96I  |
|        |        |        |        | Human mRNA for HLA-D<br>class II antigen DR1 beta |      |         |       |
| X03069 | X03069 | 142857 | GEN-PI | chain                                             | 361  | 299G>A  | R100K |
|        |        |        |        | Human mRNA for HLA-D<br>class II antigen DR1 beta |      |         |       |
| X03069 | X03069 | 142857 | GEN-PI | chain                                             | 452  | 390G>A  | S     |
|        |        |        |        | Human mRNA for HLA-D<br>class II antigen DR1 beta |      |         |       |
| X03069 | X03069 | 142857 | GEN-PI | chain                                             | 459  | 397T>G  | S133A |
|        |        |        |        | Human mRNA for HLA-D<br>class II antigen DR1 beta |      |         |       |
| X03069 | X03069 | 142857 | GEN-PI | chain                                             | 463  | 401A>G  | K134R |
|        |        |        |        | Human mRNA for HLA-D<br>class II antigen DR1 beta |      |         |       |
| X03069 | X03069 | 142857 | GEN-PI | chain                                             | 471  | 409C>A  | P137T |
|        |        |        |        | Human mRNA for HLA-D<br>class II antigen DR1 beta |      |         |       |
| X03069 | X03069 | 142857 | GEN-PI | chain                                             | 500  | 438C>T  | S     |
|        |        |        |        | Human mRNA for HLA-D<br>class II antigen DR1 beta |      |         |       |
| X03069 | X03069 | 142857 | GEN-PI | chain                                             | 508  | 446G>A  | S149N |
|        |        |        |        | Human mRNA for HLA-D<br>class II antigen DR1 beta |      |         |       |
| X03069 | X03069 | 142857 | GEN-PI | chain                                             | 523  | 461G>C  | G154A |
|        |        |        |        | Human mRNA for HLA-D<br>class II antigen DR1 beta |      |         |       |
| X03069 | X03069 | 142857 | GEN-PI | chain                                             | 547  | 485G>T  | R162L |
|        |        |        |        | Human mRNA for HLA-D<br>class II antigen DR1 beta |      |         |       |

|        |        |        |        |                                                            |     |        |       |
|--------|--------|--------|--------|------------------------------------------------------------|-----|--------|-------|
| X03069 | X03069 | 142857 | GEN-PI | Human mRNA for HLA-D<br>class II antigen DR1 beta<br>chain | 551 | 489C>T | S     |
| X03069 | X03069 | 142857 | GEN-PI | Human mRNA for HLA-D<br>class II antigen DR1 beta<br>chain | 552 | 490G>A | G164S |
| X03069 | X03069 | 142857 | GEN-PI | Human mRNA for HLA-D<br>class II antigen DR1 beta<br>chain | 567 | 505G>A | A169T |
| X03069 | X03069 | 142857 | GEN-PI | Human mRNA for HLA-D<br>class II antigen DR1 beta<br>chain | 573 | 511G>A | V171M |
| X03069 | X03069 | 142857 | GEN-PI | Human mRNA for HLA-D<br>class II antigen DR1 beta<br>chain | 584 | 522A>G | S     |
| X03069 | X03069 | 142857 | GEN-PI | Human mRNA for HLA-D<br>class II antigen DR1 beta<br>chain | 593 | 531C>T | S     |
| X03069 | X03069 | 142857 | GEN-PI | Human mRNA for HLA-D<br>class II antigen DR1 beta<br>chain | 596 | 534G>C | Q178H |
| X03069 | X03069 | 142857 | GEN-PI | Human mRNA for HLA-D<br>class II antigen DR1 beta<br>chain | 605 | 543T>C | S     |
| X03069 | X03069 | 142857 | GEN-PI | Human mRNA for HLA-D<br>class II antigen DR1 beta<br>chain | 632 | 570G>A | S     |
| X03069 | X03069 | 142857 | GEN-PI | Human mRNA for HLA-D<br>class II antigen DR1 beta<br>chain | 647 | 585G>A | S     |
| X03069 | X03069 | 142857 | GEN-PI | Human mRNA for HLA-D<br>class II antigen DR1 beta<br>chain | 686 | 624T>C | S     |
| X03069 | X03069 | 142857 | GEN-PI | Human mRNA for HLA-D<br>class II antigen DR1 beta<br>chain | 691 | 629C>T | T210M |
| X03069 | X03069 | 142857 | GEN-PI | Human mRNA for HLA-D<br>class II antigen DR1 beta<br>chain | 692 | 630G>A | S     |
| X03069 | X03069 | 142857 | GEN-PI | Human mRNA for HLA-D<br>class II antigen DR1 beta<br>chain | 716 | 654A>T | R218S |

|        |        |        |        |                                                            |      |        |       |
|--------|--------|--------|--------|------------------------------------------------------------|------|--------|-------|
| X03069 | X03069 | 142857 | GEN-PI | Human mRNA for HLA-D<br>class II antigen DR1 beta<br>chain | 721  | 659G>A | R220Q |
| X03069 | X03069 | 142857 | GEN-PI | Human mRNA for HLA-D<br>class II antigen DR1 beta<br>chain | 756  | 694G>A | V232I |
| X03069 | X03069 | 142857 | GEN-PI | Human mRNA for HLA-D<br>class II antigen DR1 beta<br>chain | 767  | 705C>T | S     |
| X03069 | X03069 | 142857 | GEN-PI | Human mRNA for HLA-D<br>class II antigen DR1 beta<br>chain | 800  | 738G>A | S     |
| X03069 | X03069 | 142857 | GEN-PI | Human mRNA for HLA-D<br>class II antigen DR1 beta<br>chain | 814  | 752G>A | R251K |
| X03069 | X03069 | 142857 | GEN-PI | Human mRNA for HLA-D<br>class II antigen DR1 beta<br>chain | 847  | 785C>G | T262R |
| X03069 | X03069 | 142857 | GEN-PI | Human mRNA for HLA-D<br>class II antigen DR1 beta<br>chain | 865  | 803A>G | 3     |
| X03069 | X03069 | 142857 | GEN-PI | Human mRNA for HLA-D<br>class II antigen DR1 beta<br>chain | 868  | 806C>A | 3     |
| X03069 | X03069 | 142857 | GEN-PI | Human mRNA for HLA-D<br>class II antigen DR1 beta<br>chain | 893  | 831C>T | 3     |
| X03069 | X03069 | 142857 | GEN-PI | Human mRNA for HLA-D<br>class II antigen DR1 beta<br>chain | 899  | 837T>C | 3     |
| X03069 | X03069 | 142857 | GEN-PI | Human mRNA for HLA-D<br>class II antigen DR1 beta<br>chain | 903  | 841A>G | 3     |
| X03069 | X03069 | 142857 | GEN-PI | Human mRNA for HLA-D<br>class II antigen DR1 beta<br>chain | 913  | 851A>G | 3     |
| X03069 | X03069 | 142857 | GEN-PI | Human mRNA for HLA-D<br>class II antigen DR1 beta<br>chain | 988  | 926G>A | 3     |
| X03069 | X03069 | 142857 | GEN-PI | Human mRNA for HLA-D<br>class II antigen DR1 beta<br>chain | 1004 | 942G>A | 3     |

|        |        |        |        |                                                              |      |         |       |
|--------|--------|--------|--------|--------------------------------------------------------------|------|---------|-------|
| X03069 | X03069 | 142857 | GEN-PI | class II antigen DR1 beta chain                              | 1027 | 965C>T  | 3     |
| X03069 | X03069 | 142857 | GEN-PI | Human mRNA for HLA-D class II antigen DR1 beta chain         | 1105 | 1043G>C | 3     |
| X03069 | X03069 | 142857 | GEN-PI | Human mRNA for HLA-D class II antigen DR1 beta chain         | 1128 | 1066C>T | 3     |
| X03069 | X03069 | 142857 | GEN-PI | Human mRNA for HLA-D class II antigen DR1 beta chain         | 1139 | 1077C>T | 3     |
| X03069 | X03069 | 142857 | GEN-PI | Human mRNA for HLA-D class II antigen DR1 beta chain         | 1140 | 1078G>C | 3     |
| X03438 | X03438 | 138970 | GEN-PM | Human mRNA for granulocyte colony-stimulating factor (G-CSF) | 586  | 555G>A  | S     |
| X03438 | X03438 | 138970 | GEN-PM | Human mRNA for granulocyte colony-stimulating factor (G-CSF) | 1235 | 1204C>T | 3     |
| X03663 | X03663 | 164770 | GEN-51 | Colony stimulating factor 1 receptor                         | 3732 | 3432T>C | 3     |
| X03663 | X03663 | 164770 | GEN-51 | Colony stimulating factor 1 receptor                         | 3951 | 3651C>A | 3     |
| X03674 | X03674 | 305900 | GEN-9K | Glucose-6-phosphate dehydrogenase                            | 503  | 33C>G   | H11Q  |
| X03674 | X03674 | 305900 | GEN-9K | Glucose-6-phosphate dehydrogenase                            | 589  | 119C>T  | S40L  |
| X03674 | X03674 | 305900 | GEN-9K | Glucose-6-phosphate dehydrogenase                            | 672  | 202G>A  | V68M  |
| X03674 | X03674 | 305900 | GEN-9K | Glucose-6-phosphate dehydrogenase                            | 846  | 376A>G  | N126D |
| X03674 | X03674 | 305900 | GEN-9K | Glucose-6-phosphate dehydrogenase                            | 2215 | 1745T>C | 3     |
| X03674 | X03674 | 305900 | GEN-9K | Glucose-6-phosphate dehydrogenase                            | 2242 | 1772T>C | 3     |
| X03674 | X03674 | 305900 | GEN-9K | Glucose-6-phosphate dehydrogenase                            | 2341 | 1871G>A | 3     |

|        |        |        |         |                                                                         |      |          |       |
|--------|--------|--------|---------|-------------------------------------------------------------------------|------|----------|-------|
| X03884 | X03884 | 186830 | GEN-52  | CD3E antigen, epsilon polypeptide (TiT3 complex)                        | 108  | 54C>T    | S     |
| X03884 | X03884 | 186830 | GEN-52  | CD3E antigen, epsilon polypeptide (TiT3 complex)                        | 1258 | 1204T>A  | 3     |
| X04391 | X04391 | None   | GEN-14D | Human mRNA for lymphocyte glycoprotein T1/Leu-1                         | 2084 | 2012G>A  | 3     |
| CD1A   | X04450 | 188370 | GEN-14J | Human CD1 mRNA fragment for HTA1 thymocyte antigen (3terminal fragment) | 402  | 402T>C   | S     |
| X04476 | X04476 | 153390 | GEN-14K | Human mRNA fragment for p56(LSTRA) protein-tyrosine kinase              | 601  | 601G>A   | 3     |
| X04571 | X04571 | 131530 | GEN-KY0 | Human mRNA for kidney epidermal growth factor (EGF) precursor           | 4507 | 4071G>A  | 3     |
| X04608 | X04608 | 104770 | GEN-PQ  | Human mRNA for serum amyloid P component (SAP)                          | 698  | 602T>C   | I201T |
| X06180 | X06180 | 186820 | GEN-19A | Human mRNA for CD7 antigen (gp40)                                       | 1121 | 1122C>T  | 3     |
| ITGA5  | X06256 | 135620 | GEN-19B | Human mRNA for fibronectin receptor alpha subunit                       | 2562 | 2539C>A  | L847I |
| X06318 | X06318 | 176970 | GEN-KY  | Protein kinase C, beta 1                                                | 83   | (-54)G>C | 5     |
| X06318 | X06318 | 176970 | GEN-KY  | Protein kinase C, beta 1                                                | 940  | 804G>A   | S     |
| X06318 | X06318 | 176970 | GEN-KY  | Protein kinase C, beta 1                                                | 1327 | 1191T>C  | S     |
| X06318 | X06318 | 176970 | GEN-KY  | Protein kinase C, beta 1                                                | 1906 | 1770C>T  | S     |
| TCRD   | X06557 | 186810 | GEN-19M | Human mRNA for TCR-delta chain                                          | 1032 | 1014C>A  | 3     |
| X07523 | X07523 | 134371 | GEN-1E5 | Human mRNA for truncated form of complement factor H                    | 1170 | 1097G>A  | G366E |
| X07523 | X07523 | 134371 | GEN-1E5 | Human mRNA for truncated form of complement factor H                    | 1277 | 1204T>C  | Y402H |
| SOD2   | X07834 | 147460 | GEN-1ES | Human mRNA for manganese superoxide dismutase (EC 1.15.1.1)             | 44   | 40C>G    | P14A  |

|        |        |        |         |                                                             |      |         |      |
|--------|--------|--------|---------|-------------------------------------------------------------|------|---------|------|
| SOD2   | X07834 | 147460 | GEN-1ES | Human mRNA for manganese superoxide dismutase (EC 1.15.1.1) | 51   | 47T>C   | V16A |
| SOD2   | X07834 | 147460 | GEN-1ES | Human mRNA for manganese superoxide dismutase (EC 1.15.1.1) | 198  | 194C>A  | T65N |
| SOD2   | X07834 | 147460 | GEN-1ES | Human mRNA for manganese superoxide dismutase (EC 1.15.1.1) | 249  | 245T>C  | I82T |
| ITGB1  | X07979 | 135630 | GEN-4E5 | Human mRNA for fibronectin receptor beta subunit            | 1189 | 1086A>C | S    |
| ITGB1  | X07979 | 135630 | GEN-4E5 | Human mRNA for fibronectin receptor beta subunit            | 1279 | 1176A>C | S    |
| ITGB1  | X07979 | 135630 | GEN-4E5 | Human mRNA for fibronectin receptor beta subunit            | 2713 | 2610T>C | 3    |
| ITGB1  | X07979 | 135630 | GEN-4E5 | Human mRNA for fibronectin receptor beta subunit            | 2878 | 2775T>A | 3    |
| ITGB1  | X07979 | 135630 | GEN-4E5 | Human mRNA for fibronectin receptor beta subunit            | 3339 | 3236A>G | 3    |
| ITGB1  | X07979 | 135630 | GEN-4E5 | Human mRNA for fibronectin receptor beta subunit            | 3531 | 3428G>A | 3    |
| ANX5   | X12454 | 131230 | GEN-1M2 | Human mRNA for vascular anticoagulant                       | 128  | (-1)C>T | 5    |
| ANX5   | X12454 | 131230 | GEN-1M2 | Human mRNA for vascular anticoagulant                       | 1413 | 1285T>G | 3    |
| ANX5   | X12454 | 131230 | GEN-1M2 | Human mRNA for vascular anticoagulant                       | 1431 | 1303C>T | 3    |
| ANX5   | X12454 | 131230 | GEN-1M2 | Human mRNA for vascular anticoagulant                       | 1518 | 1390G>A | 3    |
| X12530 | X12530 | 112210 | GEN-1MH | Human mRNA for B lymphocyte antigen CD20 (B1, Bp35)         | 131  | 38C>T   | P13L |
| X12530 | X12530 | 112210 | GEN-1MH | Human mRNA for B lymphocyte antigen CD20 (B1, Bp35)         | 1318 | 1225G>A | 3    |

|        |        |        |         |                                                              |      |         |       |
|--------|--------|--------|---------|--------------------------------------------------------------|------|---------|-------|
| X13403 | X13403 | 164175 | GEN-L8  | POU domain, class 2,<br>transcription factor 1               | 1298 | 1239T>C | S     |
| X13403 | X13403 | 164175 | GEN-L8  | POU domain, class 2,<br>transcription factor 1               | 1476 | 1417G>A | A473T |
| X13561 | X13561 | 147910 | GEN-10H | Human mRNA for<br>preprokallikrein (EC 3.4.21)               | 54   | 18G>T   | S     |
| X13561 | X13561 | 147910 | GEN-10H | Human mRNA for<br>preprokallikrein (EC 3.4.21)               | 441  | 405T>C  | S     |
| X13561 | X13561 | 147910 | GEN-10H | Human mRNA for<br>preprokallikrein (EC 3.4.21)               | 469  | 433G>C  | E145Q |
| X13561 | X13561 | 147910 | GEN-10H | Human mRNA for<br>preprokallikrein (EC 3.4.21)               | 592  | 556A>G  | K186E |
| LIF    | X13967 | 159540 | GEN-1PZ | Human mRNA for<br>leukaemia inhibitory factor<br>(LIF/HILDA) | 3710 | 3666T>G | 3     |
| X14356 | X14356 | 146760 | GEN-1R0 | Human mRNA for high<br>affinity Fc receptor (FcRI)           | 195  | 159T>C  | S     |
| X14356 | X14356 | 146760 | GEN-1R0 | Human mRNA for high<br>affinity Fc receptor (FcRI)           | 1006 | 970G>A  | D324N |
| X14356 | X14356 | 146760 | GEN-1R0 | Human mRNA for high<br>affinity Fc receptor (FcRI)           | 1161 | 1125G>A | S     |
| X14356 | X14356 | 146760 | GEN-1R0 | Human mRNA for high<br>affinity Fc receptor (FcRI)           | 1164 | 1128G>A | 3     |
| X14356 | X14356 | 146760 | GEN-1R0 | Human mRNA for high<br>affinity Fc receptor (FcRI)           | 1174 | 1138G>T | 3     |
| X14356 | X14356 | 146760 | GEN-1R0 | Human mRNA for high<br>affinity Fc receptor (FcRI)           | 1203 | 1167C>T | 3     |
| X14356 | X14356 | 146760 | GEN-1R0 | Human mRNA for high<br>affinity Fc receptor (FcRI)           | 1217 | 1181G>A | 3     |
| X14356 | X14356 | 146760 | GEN-1R0 | Human mRNA for high<br>affinity Fc receptor (FcRI)           | 1279 | 1243G>A | 3     |
| X14583 | X14583 | None   | GEN-1RJ | Human mRNA for Ig<br>lambda-chain                            | 131  | 107A>G  | K36R  |
| X14583 | X14583 | None   | GEN-1RJ | Human mRNA for Ig<br>lambda-chain                            | 132  | 108G>A  | S     |
| X14583 | X14583 | None   | GEN-1RJ | Human mRNA for Ig<br>lambda-chain                            | 164  | 140A>C  | N47T  |
| X14583 | X14583 | None   | GEN-1RJ | Human mRNA for Ig<br>lambda-chain                            | 255  | 231G>T  | S     |
| X14583 | X14583 | None   | GEN-1RJ | Human mRNA for Ig<br>lambda-chain                            | 381  | 357A>G  | S     |

|        |        |        |         |                                                       |      |          |       |
|--------|--------|--------|---------|-------------------------------------------------------|------|----------|-------|
| X14583 | X14583 | None   | GEN-1RJ | Human mRNA for Ig lambda-chain                        | 400  | 376C>G   | L126V |
| X14583 | X14583 | None   | GEN-1RJ | Human mRNA for Ig lambda-chain                        | 412  | 388G>A   | G130S |
| X14583 | X14583 | None   | GEN-1RJ | Human mRNA for Ig lambda-chain                        | 450  | 426G>A   | S     |
| X14583 | X14583 | None   | GEN-1RJ | Human mRNA for Ig lambda-chain                        | 522  | 498C>T   | S     |
| X14583 | X14583 | None   | GEN-1RJ | Human mRNA for Ig lambda-chain                        | 540  | 516G>C   | K172N |
| X14583 | X14583 | None   | GEN-1RJ | Human mRNA for Ig lambda-chain                        | 553  | 529C>A   | P177T |
| X14583 | X14583 | None   | GEN-1RJ | Human mRNA for Ig lambda-chain                        | 594  | 570A>G   | S     |
| X14583 | X14583 | None   | GEN-1RJ | Human mRNA for Ig lambda-chain                        | 624  | 600T>C   | S     |
| X14583 | X14583 | None   | GEN-1RJ | Human mRNA for Ig lambda-chain                        | 639  | 615T>C   | S     |
| X14583 | X14583 | None   | GEN-1RJ | Human mRNA for Ig lambda-chain                        | 659  | 635G>A   | R212K |
| X14583 | X14583 | None   | GEN-1RJ | Human mRNA for Ig lambda-chain                        | 738  | 714A>C   | 3     |
| X14583 | X14583 | None   | GEN-1RJ | Human mRNA for Ig lambda-chain                        | 740  | 716A>T   | 3     |
| X14583 | X14583 | None   | GEN-1RJ | Human mRNA for Ig lambda-chain                        | 752  | 728C>A   | 3     |
| X14583 | X14583 | None   | GEN-1RJ | Human mRNA for Ig lambda-chain                        | 858  | 834C>G   | 3     |
| CHRNA1 | X14830 | 100710 | GEN-4EK | Nicotinic, Cholinergic receptor beta 1                | 1375 | 1359C>T  | S     |
| CHRNA1 | X14830 | 100710 | GEN-4EK | Nicotinic, Cholinergic receptor beta 1                | 1591 | 1575T>C  | 3     |
| X15263 | X15263 | None   | GEN-4EQ | Muscarinic receptor, CHRM1                            | 1144 | 1044G>A  | S     |
| X15606 | X15606 | 146630 | GEN-20  | Intercellular adhesion molecule 2                     | 884  | 822G>A   | S     |
| IRF2   | X15949 | 147576 | GEN-1UO | Human mRNA for interferon regulatory factor-2 (IRF-2) | 842  | 744G>A   | S     |
| X16166 | X16166 | 182284 | GEN-QT  | Human mRNA for putative cytokine 21 (HC21)            | 41   | (-12)T>G | 5     |



|        |        |        |         |                                                                |     |        |      |
|--------|--------|--------|---------|----------------------------------------------------------------|-----|--------|------|
| X16166 | X16166 | 182284 | GEN-QT  | Human mRNA for putative cytokine 21 (HC21)                     | 86  | 34A>G  | M12V |
| X16166 | X16166 | 182284 | GEN-QT  | Human mRNA for putative cytokine 21 (HC21)                     | 111 | 59C>T  | P20L |
| X16166 | X16166 | 182284 | GEN-QT  | Human mRNA for putative cytokine 21 (HC21)                     | 115 | 63G>A  | S    |
| X16166 | X16166 | 182284 | GEN-QT  | Human mRNA for putative cytokine 21 (HC21)                     | 162 | 110C>T | S37F |
| X16166 | X16166 | 182284 | GEN-QT  | Human mRNA for putative cytokine 21 (HC21)                     | 260 | 208A>G | S70G |
| X16166 | X16166 | 182284 | GEN-QT  | Human mRNA for putative cytokine 21 (HC21)                     | 274 | 222T>C | S    |
| X16166 | X16166 | 182284 | GEN-QT  | Human mRNA for putative cytokine 21 (HC21)                     | 280 | 228T>C | S    |
| X16166 | X16166 | 182284 | GEN-QT  | Human mRNA for putative cytokine 21 (HC21)                     | 289 | 237A>G | S    |
| X16166 | X16166 | 182284 | GEN-QT  | Human mRNA for putative cytokine 21 (HC21)                     | 375 | 323C>T | 3    |
| X16166 | X16166 | 182284 | GEN-QT  | Human mRNA for putative cytokine 21 (HC21)                     | 393 | 341A>C | 3    |
| X16166 | X16166 | 182284 | GEN-QT  | Human mRNA for putative cytokine 21 (HC21)                     | 395 | 343A>G | 3    |
| X16166 | X16166 | 182284 | GEN-QT  | Human mRNA for putative cytokine 21 (HC21)                     | 437 | 385C>T | 3    |
| X16166 | X16166 | 182284 | GEN-QT  | Human mRNA for putative cytokine 21 (HC21)                     | 549 | 497G>C | 3    |
| CSNK2B | X16312 | 115441 | GEN-1XW | Human mRNA for cytokine 21 (HC21)                              | 271 | 138T>C | S    |
| CSNK2B | X16312 | 115441 | GEN-1XW | Human mRNA for phosphatase/casein kinase II beta subunit       | 812 | 679A>T | 3    |
| CSNK2B | X16312 | 115441 | GEN-1XW | Human mRNA for phosphatase/casein kinase II beta subunit       | 885 | 752T>C | 3    |
| X16863 | X16863 | 146740 | GEN-1YV | Human Fc-gamma RIII-1 cDNA for Fc-gamma receptor III-1 (CD 16) | 141 | 108C>G | S36R |
| X16863 | X16863 | 146740 | GEN-1YV | Human Fc-gamma RIII-1 cDNA for Fc-gamma receptor III-1 (CD 16) | 147 | 114T>C | S    |

|        |        |        |         |                                                                |      |         |       |
|--------|--------|--------|---------|----------------------------------------------------------------|------|---------|-------|
| X16863 | X16863 | 146740 | GEN-1YV | Human Fc-gamma RIII-1 cDNA for Fc-gamma receptor III-1 (CD 16) | 277  | 244A>G  | N82D  |
| X16863 | X16863 | 146740 | GEN-1YV | Human Fc-gamma RIII-1 cDNA for Fc-gamma receptor III-1 (CD 16) | 473  | 440A>G  | D147G |
| X16863 | X16863 | 146740 | GEN-1YV | Human Fc-gamma RIII-1 cDNA for Fc-gamma receptor III-1 (CD 16) | 505  | 472C>T  | H158Y |
| X16863 | X16863 | 146740 | GEN-1YV | Human Fc-gamma RIII-1 cDNA for Fc-gamma receptor III-1 (CD 16) | 531  | 498T>C  | S     |
| X16863 | X16863 | 146740 | GEN-1YV | Human Fc-gamma RIII-1 cDNA for Fc-gamma receptor III-1 (CD 16) | 559  | 526G>T  | V176F |
| X16863 | X16863 | 146740 | GEN-1YV | Human Fc-gamma RIII-1 cDNA for Fc-gamma receptor III-1 (CD 16) | 733  | 700T>C  | F     |
| X16863 | X16863 | 146740 | GEN-1YV | Human Fc-gamma RIII-1 cDNA for Fc-gamma receptor III-1 (CD 16) | 766  | 733C>T  | 3     |
| X16863 | X16863 | 146740 | GEN-1YV | Human Fc-gamma RIII-1 cDNA for Fc-gamma receptor III-1 (CD 16) | 829  | 796G>A  | 3     |
| MIC2   | X16996 | 313470 | GEN-1ZE | Human mRNA for T-cell surface glycoprotein E2                  | 210  | 87T>C   | S     |
| MIC2   | X16996 | 313470 | GEN-1ZE | Human mRNA for T-cell surface glycoprotein E2                  | 283  | 160G>A  | D54N  |
| MIC2   | X16996 | 313470 | GEN-1ZE | Human mRNA for T-cell surface glycoprotein E2                  | 486  | 363C>T  | S     |
| MIC2   | X16996 | 313470 | GEN-1ZE | Human mRNA for T-cell surface glycoprotein E2                  | 1068 | 945C>T  | 3     |
| X17033 | X17033 | 192974 | GEN-LG  | Integrin, alpha 2 (CD49B, alpha 2 subunit of VLA-2 receptor)   | 4193 | 4145T>G | 3     |
| X17033 | X17033 | 192974 | GEN-LG  | Integrin, alpha 2 (CD49B, alpha 2 subunit of VLA-2 receptor)   | 4849 | 4801A>G | 3     |
| X17033 | X17033 | 192974 | GEN-LG  | Integrin, alpha 2 (CD49B, alpha 2 subunit of VLA-2 receptor)   | 4897 | 4849A>G | 3     |

|        |        |        |         |                                                                              |      |         |       |
|--------|--------|--------|---------|------------------------------------------------------------------------------|------|---------|-------|
| X17042 | X17042 | 177040 | GEN-1ZN | Human mRNA for hematopoietic proteoglycan core protein                       | 324  | 300C>T  | S     |
| X17042 | X17042 | 177040 | GEN-1ZN | Human mRNA for hematopoietic proteoglycan core protein                       | 1021 | 997G>T  | 3     |
| IGHM   | X17115 | 147020 | GEN-1ZX | Human mRNA for IgM heavy chain complete sequence                             | 849  | 777T>C  | S     |
| IGHM   | X17115 | 147020 | GEN-1ZX | Human mRNA for IgM heavy chain complete sequence                             | 1102 | 1030A>G | S344G |
| IGHM   | X17115 | 147020 | GEN-1ZX | Human mRNA for IgM heavy chain complete sequence                             | 1107 | 1035G>A | S     |
| IGHM   | X17115 | 147020 | GEN-1ZX | Human mRNA for IgM heavy chain complete sequence                             | 1175 | 1103T>G | V368G |
| IGHM   | X17115 | 147020 | GEN-1ZX | Human mRNA for IgM heavy chain complete sequence                             | 1212 | 1140C>T | S     |
| IGHM   | X17115 | 147020 | GEN-1ZX | Human mRNA for IgM heavy chain complete sequence                             | 1561 | 1489C>G | R497G |
| IGHM   | X17115 | 147020 | GEN-1ZX | Human mRNA for IgM heavy chain complete sequence                             | 1692 | 1620G>T | Q540H |
| IGHM   | X17115 | 147020 | GEN-1ZX | Human mRNA for IgM heavy chain complete sequence                             | 1816 | 1744G>C | V582L |
| IGHM   | X17115 | 147020 | GEN-1ZX | Human mRNA for IgM heavy chain complete sequence                             | 2006 | 1934T>A | 3     |
| HLA-G  | X17273 | 142871 | GEN-205 | Human HLA G (HLA 6.0) mRNA for non classical class I transplantation antigen | 20   | 15G>A   | S     |
| HLA-G  | X17273 | 142871 | GEN-205 | Human HLA G (HLA 6.0) mRNA for non classical class I transplantation antigen | 41   | 36G>A   | S     |

|       |        |        |         |                                                                                       |      |         |   |
|-------|--------|--------|---------|---------------------------------------------------------------------------------------|------|---------|---|
| HLA-G | X17273 | 142871 | GEN-205 | Human HLA G (HLA 6.0)<br>mRNA for non classical<br>class I transplantation<br>antigen | 248  | 243G>A  | S |
| HLA-G | X17273 | 142871 | GEN-205 | Human HLA G (HLA 6.0)<br>mRNA for non classical<br>class I transplantation<br>antigen | 356  | 351C>T  | S |
| HLA-G | X17273 | 142871 | GEN-205 | Human HLA G (HLA 6.0)<br>mRNA for non classical<br>class I transplantation<br>antigen | 812  | 807A>C  | S |
| HLA-G | X17273 | 142871 | GEN-205 | Human HLA G (HLA 6.0)<br>mRNA for non classical<br>class I transplantation<br>antigen | 839  | 834G>A  | S |
| HLA-G | X17273 | 142871 | GEN-205 | Human HLA G (HLA 6.0)<br>mRNA for non classical<br>class I transplantation<br>antigen | 947  | 942C>T  | S |
| HLA-G | X17273 | 142871 | GEN-205 | Human HLA G (HLA 6.0)<br>mRNA for non classical<br>class I transplantation<br>antigen | 1004 | 999A>G  | S |
| HLA-G | X17273 | 142871 | GEN-205 | Human HLA G (HLA 6.0)<br>mRNA for non classical<br>class I transplantation<br>antigen | 1123 | 1118G>C | 3 |
| HLA-G | X17273 | 142871 | GEN-205 | Human HLA G (HLA 6.0)<br>mRNA for non classical<br>class I transplantation<br>antigen | 1140 | 1135C>A | 3 |
| HLA-G | X17273 | 142871 | GEN-205 | Human HLA G (HLA 6.0)<br>mRNA for non classical<br>class I transplantation<br>antigen | 1148 | 1143C>T | 3 |
| HLA-G | X17273 | 142871 | GEN-205 | Human HLA G (HLA 6.0)<br>mRNA for non classical<br>class I transplantation<br>antigen | 1254 | 1249T>G | 3 |
| HLA-G | X17273 | 142871 | GEN-205 | Human HLA G (HLA 6.0)<br>mRNA for non classical<br>class I transplantation<br>antigen | 1255 | 1250C>G | 3 |

|        |        |        |         |                                                        |                      |      |         |       |
|--------|--------|--------|---------|--------------------------------------------------------|----------------------|------|---------|-------|
| X51362 | X51362 | 126450 | GEN-31W | mRNA for non classical class I transplantation antigen | Dopamine Receptor D2 | 588  | 423G>A  | S     |
| X51362 | X51362 | 126450 | GEN-31W |                                                        | Dopamine Receptor D2 | 1104 | 939C>T  | S     |
| X51362 | X51362 | 126450 | GEN-31W |                                                        | Dopamine Receptor D2 | 1122 | 957T>C  | S     |
| X51362 | X51362 | 126450 | GEN-31W |                                                        | Dopamine Receptor D2 | 1248 | 1083A>G | S     |
| X51362 | X51362 | 126450 | GEN-31W |                                                        | Dopamine Receptor D2 | 1488 | 1323T>C | S     |
| X51362 | X51362 | 126450 | GEN-31W |                                                        | Dopamine Receptor D2 | 1548 | 1383A>G | 3     |
| X51362 | X51362 | 126450 | GEN-31W |                                                        | Dopamine Receptor D2 | 2361 | 2196C>T | 3     |
| EDN3   | X52001 | 131242 | GEN-33E |                                                        | Endothelin 3         | 1262 | 1152G>A | 3     |
| EDN3   | X52001 | 131242 | GEN-33E |                                                        | Endothelin 3         | 1649 | 1539C>G | 3     |
| EDN3   | X52001 | 131242 | GEN-33E |                                                        | Endothelin 3         | 1700 | 1590C>T | 3     |
| EDN3   | X52001 | 131242 | GEN-33E |                                                        | Endothelin 3         | 1742 | 1632C>T | 3     |
| EDN3   | X52001 | 131242 | GEN-33E |                                                        | Endothelin 3         | 1797 | 1687C>T | 3     |
| EDN3   | X52001 | 131242 | GEN-33E |                                                        | Endothelin 3         | 1914 | 1804G>C | 3     |
| EDN3   | X52001 | 131242 | GEN-33E |                                                        | Endothelin 3         | 2040 | 1930C>T | 3     |
| X52079 | X52079 | 602272 | GEN-33B | H.sapiens transcription factor (ITF-2) mRNA, 3 end     |                      | 979  | 979T>G  | S327A |
| X52079 | X52079 | 602272 | GEN-33B | H.sapiens transcription factor (ITF-2) mRNA, 3 end     |                      | 1794 | 1794G>A | S     |
| X52425 | X52425 | 147781 | GEN-59  | Interleukin 4 receptor                                 |                      | 3044 | 2869G>A | 3     |
| X52425 | X52425 | 147781 | GEN-59  | Interleukin 4 receptor                                 |                      | 3289 | 3114A>G | 3     |
| X52425 | X52425 | 147781 | GEN-59  | Interleukin 4 receptor                                 |                      | 3391 | 3216C>T | 3     |
| X52479 | X52479 | 176960 | GEN-LM  | Protein kinase C, alpha                                |                      | 908  | 881A>C  | D294A |
| CD22   | X52785 | 107266 | GEN-33Z | H.sapiens CD22 mRNA                                    |                      | 1357 | 1323C>T | S     |

|        |        |        |         |                                                 |      |         |      |
|--------|--------|--------|---------|-------------------------------------------------|------|---------|------|
| CD22   | X52785 | 107266 | GEN-33Z | H.sapiens CD22 mRNA                             | 1531 | 1497C>T | S    |
| CHRNA3 | X53559 | 118503 | GEN-34I | Nicotinic, Cholinergic receptor alpha 3         | 212  | 212A>G  | D71G |
| CHRNA3 | X53559 | 118503 | GEN-34I | Nicotinic, Cholinergic receptor alpha 3         | 552  | 552C>T  | S    |
| KAI1   | X53795 | 600623 | GEN-34P | Human R2 mRNA for an inducible membrane protein | 510  | 354C>T  | S    |
| KAI1   | X53795 | 600623 | GEN-34P | Human R2 mRNA for an inducible membrane protein | 1196 | 1040G>T | 3    |
| KAI1   | X53795 | 600623 | GEN-34P | Human R2 mRNA for an inducible membrane protein | 1309 | 1153G>A | 3    |
| KAI1   | X53795 | 600623 | GEN-34P | Human R2 mRNA for an inducible membrane protein | 1325 | 1169G>A | 3    |
| KAI1   | X53795 | 600623 | GEN-34P | Human R2 mRNA for an inducible membrane protein | 1335 | 1179G>A | 3    |
| KAI1   | X53795 | 600623 | GEN-34P | Human R2 mRNA for an inducible membrane protein | 1362 | 1206C>T | 3    |
| KAI1   | X53795 | 600623 | GEN-34P | Human R2 mRNA for an inducible membrane protein | 1367 | 1211C>T | 3    |
| KAI1   | X53795 | 600623 | GEN-34P | Human R2 mRNA for an inducible membrane protein | 1368 | 1212G>A | 3    |
| KAI1   | X53795 | 600623 | GEN-34P | Human R2 mRNA for an inducible membrane protein | 1370 | 1214G>A | 3    |
| KAI1   | X53795 | 600623 | GEN-34P | Human R2 mRNA for an inducible membrane protein | 1371 | 1215T>C | 3    |
| KAI1   | X53795 | 600623 | GEN-34P | Human R2 mRNA for an inducible membrane protein | 1378 | 1222C>T | 3    |
| KAI1   | X53795 | 600623 | GEN-34P | Human R2 mRNA for an inducible membrane protein | 1382 | 1226G>A | 3    |

|        |        |        |         |                                                                                                                            |      |          |       |
|--------|--------|--------|---------|----------------------------------------------------------------------------------------------------------------------------|------|----------|-------|
| KAI1   | X53795 | 600623 | GEN-34P | Human R2 mRNA for an inducible membrane protein                                                                            | 1392 | 1236C>T  | 3     |
| KAI1   | X53795 | 600623 | GEN-34P | Human R2 mRNA for an inducible membrane protein                                                                            | 1423 | 1267C>T  | 3     |
| X54101 | X54101 | None   | GEN-34W | Human NKG5 mRNA, expressed in natural killer cells and T-cells                                                             | 484  | 356C>T   | T119I |
| X54101 | X54101 | None   | GEN-34W | Human NKG5 mRNA, expressed in natural killer cells and T-cells                                                             | 625  | 497C>G   | 3     |
| X54101 | X54101 | None   | GEN-34W | Human NKG5 mRNA, expressed in natural killer cells and T-cells                                                             | 717  | 589C>G   | 3     |
| FCAR   | X54150 | 147045 | GEN-34T | Human mRNA for Fc receptor                                                                                                 | 363  | 324A>G   | S     |
| X54199 | X54199 | 138440 | GEN-LS  | Phosphoribosylglycinamide formyltransferase, phosphoribosylglycinamide synthetase, phosphoribosylaminoimidazole synthetase | 168  | 90G>A    | S     |
| X54315 | X54315 | 114020 | GEN-351 | Human mRNA for N-cadherin                                                                                                  | 2549 | 2448T>C  | S     |
| X54867 | X54867 | 161555 | GEN-MIV | Human mRNA for NKG2-A gene                                                                                                 | 1188 | 1024G>C  | 3     |
| X54867 | X54867 | 161555 | GEN-MIV | Human mRNA for NKG2-A gene                                                                                                 | 1214 | 1050T>A  | 3     |
| X54867 | X54867 | 161555 | GEN-MIV | Human mRNA for NKG2-A gene                                                                                                 | 1232 | 1068A>T  | 3     |
| X54867 | X54867 | 161555 | GEN-MIV | Human mRNA for NKG2-A gene                                                                                                 | 1269 | 1105G>A  | 3     |
| X54867 | X54867 | 161555 | GEN-MIV | Human mRNA for NKG2-A gene                                                                                                 | 1353 | 1189C>T  | 3     |
| X55415 | X55415 | 137060 | GEN-364 | Human mRNA for UDP_galactose:N-acetylglucosaminide-(beta 1->4) galactosyltransferase                                       | 28   | (-12)G>C | 5     |

|        |        |        |             |                                                                                                   |      |          |       |
|--------|--------|--------|-------------|---------------------------------------------------------------------------------------------------|------|----------|-------|
| X55415 | X55415 | 137060 | GEN-364     | Human mRNA for<br>UDP_galactose:N-<br>acetylglucosaminide-(beta<br>1->4)                          | 30   | (-10)C>G | 5     |
| X55415 | X55415 | 137060 | GEN-364     | galactosyltransferase<br>Human mRNA for<br>UDP_galactose:N-<br>acetylglucosaminide-(beta<br>1->4) | 531  | 492G>A   | S     |
| X55415 | X55415 | 137060 | GEN-364     | galactosyltransferase<br>Human mRNA for<br>UDP_galactose:N-<br>acetylglucosaminide-(beta<br>1->4) | 770  | 731A>G   | H244R |
| X55415 | X55415 | 137060 | GEN-364     | galactosyltransferase<br>Human mRNA for<br>UDP_galactose:N-<br>acetylglucosaminide-(beta<br>1->4) | 1041 | 1002G>A  | S     |
| X55740 | X55740 | 129190 | GEN-<br>36H | galactosyltransferase<br>Human placental cDNA<br>coding for 5nucleotidase<br>(EC 3.1.3.5)         | 3373 | 3324T>G  | 3     |
| CRP    | X56692 | 123260 | GEN-373     | H.sapiens mRNA for C-<br>reactive protein                                                         | 330  | 241A>G   | I81V  |
| CRP    | X56692 | 123260 | GEN-373     | H.sapiens mRNA for C-<br>reactive protein                                                         | 636  | 547G>A   | V183M |
| CRP    | X56692 | 123260 | GEN-373     | H.sapiens mRNA for C-<br>reactive protein                                                         | 1020 | 931G>A   | 3     |
| YWHAB  | X57346 | 601289 | GEN-<br>37R | H.sapiens mRNA for HS1<br>protein                                                                 | 432  | 60C>A    | S     |
| YWHAB  | X57346 | 601289 | GEN-<br>37R | H.sapiens mRNA for HS1<br>protein                                                                 | 1135 | 763T>C   | 3     |
| X57348 | X57348 | 601290 | GEN-<br>37S | H.sapiens mRNA (clone<br>9112)                                                                    | 1317 | 1152C>T  | 3     |
| X57348 | X57348 | 601290 | GEN-<br>37S | H.sapiens mRNA (clone<br>9112)                                                                    | 1342 | 1177C>T  | 3     |
| X57522 | X57522 | 170260 | GEN-<br>37W | H.sapiens RING4 cDNA                                                                              | 1207 | 1177A>G  | I393V |
| X57522 | X57522 | 170260 | GEN-<br>37W | H.sapiens RING4 cDNA                                                                              | 2120 | 2090A>G  | D697G |



|        |        |        |         |                                                            |      |         |       |
|--------|--------|--------|---------|------------------------------------------------------------|------|---------|-------|
| X57819 | X57819 | None   | GEN-389 | Human rearranged immunoglobulin lambda light chain mRNA    | 499  | 499T>C  | C167R |
| X57819 | X57819 | None   | GEN-389 | Human rearranged immunoglobulin lambda light chain mRNA    | 524  | 524G>A  | F     |
| X57819 | X57819 | None   | GEN-389 | Human rearranged immunoglobulin lambda light chain mRNA    | 545  | 545G>A  | S182N |
| X57819 | X57819 | None   | GEN-389 | Human rearranged immunoglobulin lambda light chain mRNA    | 558  | 558A>C  | Q186H |
| X57819 | X57819 | None   | GEN-389 | Human rearranged immunoglobulin lambda light chain mRNA    | 571  | 571G>A  | E191K |
| X57819 | X57819 | None   | GEN-389 | Human rearranged immunoglobulin lambda light chain mRNA    | 616  | 616C>T  | F     |
| X57819 | X57819 | None   | GEN-389 | Human rearranged immunoglobulin lambda light chain mRNA    | 639  | 639G>A  | S     |
| X57819 | X57819 | None   | GEN-389 | Human rearranged immunoglobulin lambda light chain mRNA    | 695  | 695A>G  | Y232C |
| X57819 | X57819 | None   | GEN-389 | Human rearranged immunoglobulin lambda light chain mRNA    | 714  | 714C>T  | 3     |
| X57819 | X57819 | None   | GEN-389 | Human rearranged immunoglobulin lambda light chain mRNA    | 724  | 724C>T  | 3     |
| X57830 | X57830 | 182135 | GEN-7V  | Serotonin 5-HT2 receptor                                   | 247  | 102T>C  | S     |
| X58377 | X58377 | 147681 | GEN-38V | Interleukin 11                                             | 807  | 744A>G  | 3     |
| X58377 | X58377 | 147681 | GEN-38V | Interleukin 11                                             | 927  | 864T>G  | 3     |
| X58377 | X58377 | 147681 | GEN-38V | Interleukin 11                                             | 1964 | 1901T>C | 3     |
| BTK    | X58957 | 300300 | GEN-39A | H.sapiens atk mRNA for agammaglobulinaemia tyrosine kinase | 2228 | 2096A>C | 3     |
| BTK    | X58957 | 300300 | GEN-    | H.sapiens atk mRNA for                                     | 2304 | 2172A>G | 3     |

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|        |        |        |         |                                                                         |      |         |       |
|--------|--------|--------|---------|-------------------------------------------------------------------------|------|---------|-------|
| X60069 | X60069 | 231950 | GEN-3AJ | glutamyltransferase Human mRNA for pancreatic gamma-glutamyltransferase | 1624 | 1266C>T | S     |
| X60069 | X60069 | 231950 | GEN-3AJ | glutamyltransferase Human mRNA for pancreatic gamma-glutamyltransferase | 1637 | 1279C>A | P427T |
| X60069 | X60069 | 231950 | GEN-3AJ | glutamyltransferase Human mRNA for pancreatic gamma-glutamyltransferase | 1651 | 1293C>T | S     |
| X60069 | X60069 | 231950 | GEN-3AJ | glutamyltransferase Human mRNA for pancreatic gamma-glutamyltransferase | 1662 | 1304T>C | V435A |
| X60069 | X60069 | 231950 | GEN-3AJ | glutamyltransferase Human mRNA for pancreatic gamma-glutamyltransferase | 1783 | 1425A>G | S     |
| X60069 | X60069 | 231950 | GEN-3AJ | glutamyltransferase Human mRNA for pancreatic gamma-glutamyltransferase | 1794 | 1436C>T | T479M |
| X60069 | X60069 | 231950 | GEN-3AJ | glutamyltransferase Human mRNA for pancreatic gamma-glutamyltransferase | 1795 | 1437G>A | S     |
| X60069 | X60069 | 231950 | GEN-3AJ | glutamyltransferase Human mRNA for pancreatic gamma-glutamyltransferase | 1981 | 1623C>T | S     |
| X60069 | X60069 | 231950 | GEN-3AJ | glutamyltransferase Human mRNA for pancreatic gamma-glutamyltransferase | 2007 | 1649C>T | T550M |
| X60069 | X60069 | 231950 | GEN-3AJ | glutamyltransferase Human mRNA for pancreatic gamma-glutamyltransferase | 2031 | 1673C>T | S558L |
| X60069 | X60069 | 231950 | GEN-3AJ | glutamyltransferase Human mRNA for pancreatic gamma-glutamyltransferase | 2047 | 1689C>T | S     |
| X60069 | X60069 | 231950 | GEN-3AJ | glutamyltransferase Human mRNA for pancreatic gamma-glutamyltransferase | 2147 | 1789C>T | 3     |
| X60069 | X60069 | 231950 | GEN-3AJ | glutamyltransferase Human mRNA for pancreatic gamma-glutamyltransferase | 2176 | 1818C>T | 3     |
| X60069 | X60069 | 231950 | GEN-3AJ | glutamyltransferase Human mRNA for pancreatic gamma-glutamyltransferase | 2224 | 1866C>A | 3     |

|        |        |        |         |     |                                                                              |      |         |       |
|--------|--------|--------|---------|-----|------------------------------------------------------------------------------|------|---------|-------|
| X60992 | X60992 | 186720 | GEN-3BI | 3AJ | pancreatic gamma-glutamyltransferase                                         | 2556 | 2436T>C | 3     |
| X61157 | X61157 | 109635 | GEN-23  |     | H.sapiens CD6 mRNA for T cell glycoprotein CD6                               | 203  | 96A>C   | S     |
| X61157 | X61157 | 109635 | GEN-23  |     | Adrenergic receptor (Beta kinase 1-phosphorylates beta adrenergic receptor ) | 1372 | 1265A>G | H422R |
| X61157 | X61157 | 109635 | GEN-23  |     | Adrenergic receptor (Beta kinase 1-phosphorylates beta adrenergic receptor ) | 1501 | 1394G>A | R465K |
| X61157 | X61157 | 109635 | GEN-23  |     | Adrenergic receptor (Beta kinase 1-phosphorylates beta adrenergic receptor ) | 1766 | 1659C>T | S     |
| X61157 | X61157 | 109635 | GEN-23  |     | Adrenergic receptor (Beta kinase 1-phosphorylates beta adrenergic receptor ) | 1823 | 1716T>C | S     |
| X61157 | X61157 | 109635 | GEN-23  |     | Adrenergic receptor (Beta kinase 1-phosphorylates beta adrenergic receptor ) | 2976 | 2869G>A | 3     |
| NFKB2  | X61498 | 164012 | GEN-3BW |     | Adrenergic receptor (Beta kinase 1-phosphorylates beta adrenergic receptor ) | 2457 | 2294C>T | P765L |
| KDR    | X61656 | 191306 | GEN-3BZ |     | H.sapiens mRNA for NF-kB subunit                                             | 2308 | 2308A>G | T770A |
| KDR    | X61656 | 191306 | GEN-3BZ |     | H.sapiens mRNA for growth factor receptor tyrosine kinase                    | 2353 | 2353G>C | G785R |
| KDR    | X61656 | 191306 | GEN-3BZ |     | H.sapiens mRNA for growth factor receptor tyrosine kinase                    | 2499 | 2499C>G | N833K |
| KDR    | X61656 | 191306 | GEN-3BZ |     | H.sapiens mRNA for growth factor receptor tyrosine kinase                    | 2537 | 2537A>T | E846V |
| KDR    | X61656 | 191306 | GEN-3BZ |     | H.sapiens mRNA for growth factor receptor tyrosine kinase                    | 4123 | 4123G>C | 3     |
| X62572 | X62572 | 146790 | GEN-3CL |     | H.sapiens RNA for Fc receptor, PC23                                          | 967  | 968T>C  | 3     |

|        |        |        |         |                                                            |      |         |       |
|--------|--------|--------|---------|------------------------------------------------------------|------|---------|-------|
| X62572 | X62572 | 146790 | GEN-3CL | H.sapiens RNA for Fc receptor, PC23                        | 1240 | 1241A>G | 3     |
| X62572 | X62572 | 146790 | GEN-3CL | H.sapiens RNA for Fc receptor, PC23                        | 1300 | 1301C>T | 3     |
| X62572 | X62572 | 146790 | GEN-3CL | H.sapiens RNA for Fc receptor, PC23                        | 1542 | 1543G>C | 3     |
| X62572 | X62572 | 146790 | GEN-3CL | H.sapiens RNA for Fc receptor, PC23                        | 1560 | 1561C>A | 3     |
| X62572 | X62572 | 146790 | GEN-3CL | H.sapiens RNA for Fc receptor, PC23                        | 1709 | 1710T>G | 3     |
| X62572 | X62572 | 146790 | GEN-3CL | H.sapiens RNA for Fc receptor, PC23                        | 1931 | 1932A>T | 3     |
| X62572 | X62572 | 146790 | GEN-3CL | H.sapiens RNA for Fc receptor, PC23                        | 2032 | 2033G>A | 3     |
| X62572 | X62572 | 146790 | GEN-3CL | H.sapiens RNA for Fc receptor, PC23                        | 2136 | 2137G>A | 3     |
| X62572 | X62572 | 146790 | GEN-3CL | H.sapiens RNA for Fc receptor, PC23                        | 2176 | 2177C>T | 3     |
| X62572 | X62572 | 146790 | GEN-3CL | H.sapiens RNA for Fc receptor, PC23                        | 2201 | 2202G>A | 3     |
| X62744 | X62744 | 142855 | GEN-3CQ | Human RING6 mRNA for HLA class II alpha chain-like product | 541  | 496G>A  | V166I |
| X62744 | X62744 | 142855 | GEN-3CQ | Human RING6 mRNA for HLA class II alpha chain-like product | 674  | 629G>A  | R210H |
| X62744 | X62744 | 142855 | GEN-3CQ | Human RING6 mRNA for HLA class II alpha chain-like product | 750  | 705G>C  | S     |
| X62744 | X62744 | 142855 | GEN-3CQ | Human RING6 mRNA for HLA class II alpha chain-like product | 1081 | 1036A>T | 3     |
| X63053 | X63053 | 602492 | GEN-3D4 | H.sapiens PTX3 mRNA                                        | 1689 | 1684G>A | 3     |
| TCRB   | X63456 | 186930 | GEN-3DG | H.sapiens mRNA for T-cell antigen receptor beta-chain      | 421  | 411G>C  | K137N |
| TCRB   | X63456 | 186930 | GEN-3DG | H.sapiens mRNA for T-cell antigen receptor beta-chain      | 496  | 486G>A  | S     |
| TCRB   | X63456 | 186930 | GEN-    | H.sapiens mRNA for T-cell                                  | 516  | 506T>A  | F169Y |

|        |         |        |        |                                                       |      |         |       |
|--------|---------|--------|--------|-------------------------------------------------------|------|---------|-------|
| TCRB   | X63456  | 186930 | 3DG    | antigen receptor beta-chain                           | 520  | 510C>T  | S     |
|        | GEN-3DG |        |        | H.sapiens mRNA for T-cell antigen receptor beta-chain |      |         |       |
| TCRB   | X63456  | 186930 | 3DG    | antigen receptor beta-chain                           | 580  | 570A>G  | S     |
|        | GEN-3DG |        |        | H.sapiens mRNA for T-cell antigen receptor beta-chain |      |         |       |
| TCRB   | X63456  | 186930 | 3DG    | antigen receptor beta-chain                           | 754  | 744C>T  | S     |
|        | GEN-3DG |        |        | H.sapiens mRNA for T-cell antigen receptor beta-chain |      |         |       |
| TCRB   | X63456  | 186930 | 3DG    | antigen receptor beta-chain                           | 805  | 795T>C  | S     |
|        | GEN-3DG |        |        | H.sapiens mRNA for T-cell antigen receptor beta-chain |      |         |       |
| TCRB   | X63456  | 186930 | 3DG    | antigen receptor beta-chain                           | 811  | 801G>C  | S     |
|        | GEN-3DG |        |        | H.sapiens mRNA for T-cell antigen receptor beta-chain |      |         |       |
| TCRB   | X63456  | 186930 | 3DG    | antigen receptor beta-chain                           | 813  | 803T>A  | V268E |
|        | GEN-3DG |        |        | H.sapiens mRNA for T-cell antigen receptor beta-chain |      |         |       |
| TCRB   | X63456  | 186930 | 3DG    | antigen receptor beta-chain                           | 817  | 807C>T  | S     |
|        | GEN-3DG |        |        | H.sapiens mRNA for T-cell antigen receptor beta-chain |      |         |       |
| TCRB   | X63456  | 186930 | 3DG    | antigen receptor beta-chain                           | 860  | 850C>T  | S     |
|        | GEN-3DG |        |        | H.sapiens mRNA for T-cell antigen receptor beta-chain |      |         |       |
| TCRB   | X63456  | 186930 | 3DG    | antigen receptor beta-chain                           | 878  | 868C>A  | L290M |
|        | GEN-3DG |        |        | H.sapiens mRNA for T-cell antigen receptor beta-chain |      |         |       |
| X65019 | X65019  | 147678 | GEN-6G | INTERLEUKIN 1 BETA CONVERTASE PRECURSOR               | 51   | 44G>A   | R15H  |
| X65019 | X65019  | 147678 | GEN-6G | INTERLEUKIN 1 BETA CONVERTASE PRECURSOR               | 116  | 109A>C  | K37Q  |
| X65019 | X65019  | 147678 | GEN-6G | INTERLEUKIN 1 BETA CONVERTASE PRECURSOR               | 261  | 254G>A  | G85E  |
| X66403 | X66403  | 100725 | GEN-5D | Nicotinic, Cholinergic receptor epsilon polypeptide   | 2236 | 2225G>T | 3     |

|        |        |        |         |                                                           |      |         |       |
|--------|--------|--------|---------|-----------------------------------------------------------|------|---------|-------|
| X66403 | X66403 | 100725 | GEN-5D  | Nicotinic, Cholinergic<br>receptor epsilon<br>polypeptide | 2333 | 2322A>G | 3     |
| X66403 | X66403 | 100725 | GEN-5D  | Nicotinic, Cholinergic<br>receptor epsilon<br>polypeptide | 2364 | 2353G>T | 3     |
| CD44   | X66733 | 107269 | GEN-3H2 | H.sapiens mRNA for<br>epican                              | 384  | 255C>T  | S     |
| CD44   | X66733 | 107269 | GEN-3H2 | H.sapiens mRNA for<br>epican                              | 455  | 326C>A  | S109Y |
| X67325 | X67325 | 600009 | GEN-25  | Interferon alpha inducible<br>protein 27                  | 311  | 257G>A  | S86N  |
| X67325 | X67325 | 600009 | GEN-25  | Interferon alpha inducible<br>protein 27                  | 320  | 266G>C  | G89A  |
| X67325 | X67325 | 600009 | GEN-25  | Interferon alpha inducible<br>protein 27                  | 485  | 431C>G  | 3     |
| X67699 | X67699 | 114280 | GEN-3HP | H.sapiens HE5 mRNA for<br>CDw52 antigen                   | 143  | 119G>A  | S40N  |
| X67699 | X67699 | 114280 | GEN-3HP | H.sapiens HE5 mRNA for<br>CDw52 antigen                   | 147  | 123G>A  | M41I  |
| X68596 | X68596 | 168468 | GEN-3IJ | H.sapiens mRNA for<br>parathyroid hormone<br>receptor     | 1563 | 1389T>C | S     |
| X69117 | X69117 | 109636 | GEN-5G  | BETA-ADRENERGIC<br>RECEPTOR KINASE 2                      | 1182 | 1182T>C | S     |
| X69117 | X69117 | 109636 | GEN-5G  | BETA-ADRENERGIC<br>RECEPTOR KINASE 2                      | 1609 | 1609G>A | E537K |
| X69819 | X69819 | 146631 | GEN-28  | Intercellular adhesion<br>molecule 3                      | 195  | 187A>G  | I63V  |
| X69819 | X69819 | 146631 | GEN-28  | Intercellular adhesion<br>molecule 3                      | 317  | 309C>T  | S     |
| X69819 | X69819 | 146631 | GEN-28  | Intercellular adhesion<br>molecule 3                      | 436  | 428G>A  | G143D |
| X69819 | X69819 | 146631 | GEN-28  | Intercellular adhesion<br>molecule 3                      | 1172 | 1164G>A | S     |
| X69819 | X69819 | 146631 | GEN-28  | Intercellular adhesion<br>molecule 3                      | 1219 | 1211G>A | R404Q |
| X70340 | X70340 | 190170 | GEN-S3  | H.sapiens mRNA for<br>transforming growth factor<br>alpha | 3756 | 3725C>G | 3     |
| X70811 | X70811 | 109691 | GEN-    | beta-3-adrenergic receptor                                | 315  | 190T>C  | W64R  |

|        |        |        |                |                                                            |      |         |       |
|--------|--------|--------|----------------|------------------------------------------------------------|------|---------|-------|
| X70811 | X70811 | 109691 | 3KK<br>GEN-    | beta-3-adrenergic receptor                                 | 315  | 190T>C  | W64R  |
| ENG    | X72012 | 131195 | 3KK<br>GEN-3L3 | H.sapiens end mRNA for endoglin                            | 1165 | 884C>G  | T295R |
| NOS2A  | X73029 | 163730 | GEN-3LW        | H.sapiens mRNA for nitric oxide synthase                   | 1380 | 1155C>T | S     |
| NOS2A  | X73029 | 163730 | GEN-3LW        | H.sapiens mRNA for nitric oxide synthase                   | 1503 | 1278C>T | S     |
| NOS2A  | X73029 | 163730 | GEN-3LW        | H.sapiens mRNA for nitric oxide synthase                   | 2048 | 1823C>T | S608L |
| NOS2A  | X73029 | 163730 | GEN-3LW        | H.sapiens mRNA for nitric oxide synthase                   | 2287 | 2062G>A | G688S |
| NOS2A  | X73029 | 163730 | GEN-3LW        | H.sapiens mRNA for nitric oxide synthase                   | 2339 | 2114A>G | D705G |
| NOS2A  | X73029 | 163730 | GEN-3LW        | H.sapiens mRNA for nitric oxide synthase                   | 2583 | 2358T>C | S     |
| NOS2A  | X73029 | 163730 | GEN-3LW        | H.sapiens mRNA for nitric oxide synthase                   | 2982 | 2757A>G | S     |
| NOS2A  | X73029 | 163730 | GEN-3LW        | H.sapiens mRNA for nitric oxide synthase                   | 3022 | 2797C>G | R933G |
| NOS2A  | X73029 | 163730 | GEN-3LW        | H.sapiens mRNA for nitric oxide synthase                   | 3051 | 2826C>T | S     |
| NOS2A  | X73029 | 163730 | GEN-3LW        | H.sapiens mRNA for nitric oxide synthase                   | 3693 | 3468T>C | 3     |
| NOS2A  | X73029 | 163730 | GEN-3LW        | H.sapiens mRNA for nitric oxide synthase                   | 3715 | 3490G>A | 3     |
| RGS1   | X73427 | 600323 | GEN-3M6        | H.sapiens 1r20 mRNA for alpha helical basic phosphoprotein | 247  | 233C>T  | A78V  |
| MHC2TA | X74301 | 600005 | GEN-3N5        | H.sapiens mRNA for MHC class II transactivator             | 1614 | 1499C>G | A500G |
| MHC2TA | X74301 | 600005 | GEN-3N5        | H.sapiens mRNA for MHC class II transactivator             | 3759 | 3644G>A | 3     |
| MHC2TA | X74301 | 600005 | GEN-3N5        | H.sapiens mRNA for MHC class II transactivator             | 4422 | 4307T>C | 3     |
| X75913 | X75913 | 601269 | GEN-3OG        | H.sapiens mRNA for gC1q-R                                  | 1052 | 974A>G  | 3     |
| X75913 | X75913 | 601269 | GEN-3OG        | H.sapiens mRNA for gC1q-R                                  | 1074 | 996T>C  | 3     |
| X75962 | X75962 | 600315 | GEN-           | H.sapiens mRNA for OX40                                    | 836  | 831C>T  | S     |

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|        |        |        |                |                                                                  |      |         |       |
|--------|--------|--------|----------------|------------------------------------------------------------------|------|---------|-------|
| LIPA   | X76488 | 278000 | MNA<br>GEN-3P2 | homologue<br>H.sapiens mRNA for<br>lysosomal acid lipase         | 191  | 46A>C   | T16P  |
| LIPA   | X76488 | 278000 | GEN-3P2        | H.sapiens mRNA for<br>lysosomal acid lipase                      | 212  | 67G>A   | G23R  |
| LIPA   | X76488 | 278000 | GEN-3P2        | H.sapiens mRNA for<br>lysosomal acid lipase                      | 967  | 822G>A  | M274I |
| LIPA   | X76488 | 278000 | GEN-3P2        | H.sapiens mRNA for<br>lysosomal acid lipase                      | 1531 | 1386C>T | 3     |
| LIPA   | X76488 | 278000 | GEN-3P2        | H.sapiens mRNA for<br>lysosomal acid lipase                      | 2254 | 2109A>T | 3     |
| LIPA   | X76488 | 278000 | GEN-3P2        | H.sapiens mRNA for<br>lysosomal acid lipase                      | 2439 | 2294C>T | 3     |
| X77130 | X77130 | 602548 | GEN-4FN        | H.sapiens mRNA for ORL1<br>receptor                              | 528  | 351G>A  | S     |
| X77130 | X77130 | 602548 | GEN-4FN        | H.sapiens mRNA for ORL1<br>receptor                              | 569  | 392A>G  | Y131C |
| X77130 | X77130 | 602548 | GEN-4FN        | H.sapiens mRNA for ORL1<br>receptor                              | 687  | 510C>T  | S     |
| X77130 | X77130 | 602548 | GEN-4FN        | H.sapiens mRNA for ORL1<br>receptor                              | 1303 | 1126C>G | 3     |
| X77130 | X77130 | 602548 | GEN-4FN        | H.sapiens mRNA for ORL1<br>receptor                              | 1601 | 1424T>G | 3     |
| X77130 | X77130 | 602548 | GEN-4FN        | H.sapiens mRNA for ORL1<br>receptor                              | 1816 | 1639G>T | 3     |
| X77722 | X77722 | 602376 | GEN-29         | Interferon (alpha,beta,<br>omega) receptor 2 (splice<br>variant) | 253  | 28G>T   | V10F  |
| X77722 | X77722 | 602376 | GEN-29         | Interferon (alpha,beta,<br>omega) receptor 2 (splice<br>variant) | 1128 | 903A>G  | S     |
| ID1    | X77956 | 600349 | GEN-3QL        | H.sapiens Id1 mRNA                                               | 380  | 345G>A  | S     |
| ID1    | X77956 | 600349 | GEN-3QL        | H.sapiens Id1 mRNA                                               | 382  | 347C>A  | T116N |
| ID1    | X77956 | 600349 | GEN-3QL        | H.sapiens Id1 mRNA                                               | 842  | 807A>C  | 3     |
| ID1    | X77956 | 600349 | GEN-3QL        | H.sapiens Id1 mRNA                                               | 851  | 816G>A  | 3     |
| YWHAH  | X78138 | 113508 | GEN-3QU        | H.sapiens 14-3-3 eta<br>subtype mRNA                             | 953  | 753A>G  | 3     |

|        |        |        |         |                                                               |      |         |   |
|--------|--------|--------|---------|---------------------------------------------------------------|------|---------|---|
| YWHAH  | X78138 | 113508 | GEN-3QU | H.sapiens 14-3-3 eta subtype mRNA                             | 960  | 760G>A  | 3 |
| YWHAH  | X78138 | 113508 | GEN-3QU | H.sapiens 14-3-3 eta subtype mRNA                             | 1387 | 1187C>T | 3 |
| X78282 | X78282 | 601292 | GEN-LVF | H.sapiens mRNA for aryl sulfotransferase (ST1A2)              | 895  | 895T>C  | 3 |
| X78706 | X78706 | 600184 | GEN-2A  | Carnitine Acetyltransferase                                   | 1922 | 1922G>A | 3 |
| X78706 | X78706 | 600184 | GEN-2A  | Carnitine Acetyltransferase                                   | 2378 | 2378G>A | 3 |
| X78706 | X78706 | 600184 | GEN-2A  | Carnitine Acetyltransferase                                   | 2382 | 2382G>A | 3 |
| X79483 | X79483 | 602399 | GEN-LPR | H.sapiens ERK6 mRNA for extracellular signal regulated kinase | 1287 | 1254T>G | 3 |
| X80200 | X80200 | None   | GEN-3UL | H.sapiens MLN62 mRNA                                          | 1581 | 1496C>A | 3 |
| X80200 | X80200 | None   | GEN-3UL | H.sapiens MLN62 mRNA                                          | 1684 | 1599G>A | 3 |
| IGHG3  | X81695 | 147120 | GEN-3W4 | H.sapiens rearranged IgG VH-D-JH-Hinge-CH2-CH3 region         | 528  | 529C>T  | 3 |
| IGHG3  | X81695 | 147120 | GEN-3W4 | H.sapiens rearranged IgG VH-D-JH-Hinge-CH2-CH3 region         | 534  | 535C>T  | 3 |
| IGHG3  | X81695 | 147120 | GEN-3W4 | H.sapiens rearranged IgG VH-D-JH-Hinge-CH2-CH3 region         | 594  | 595T>C  | 3 |
| IGHG3  | X81695 | 147120 | GEN-3W4 | H.sapiens rearranged IgG VH-D-JH-Hinge-CH2-CH3 region         | 601  | 602A>C  | 3 |
| IGHG3  | X81695 | 147120 | GEN-3W4 | H.sapiens rearranged IgG VH-D-JH-Hinge-CH2-CH3 region         | 668  | 669A>T  | 3 |
| IGHG3  | X81695 | 147120 | GEN-3W4 | H.sapiens rearranged IgG VH-D-JH-Hinge-CH2-CH3 region         | 726  | 727T>C  | 3 |
| IGHG3  | X81695 | 147120 | GEN-3W4 | H.sapiens rearranged IgG VH-D-JH-Hinge-CH2-CH3 region         | 796  | 797G>A  | 3 |
| IGHG3  | X81695 | 147120 | GEN-3W4 | H.sapiens rearranged IgG VH-D-JH-Hinge-CH2-CH3 region         | 804  | 805G>A  | 3 |
| IGHG3  | X81695 | 147120 | GEN-3W4 | H.sapiens rearranged IgG VH-D-JH-Hinge-CH2-CH3 region         | 827  | 828A>T  | 3 |

|       |        |        |             |                                                             |      |         |   |
|-------|--------|--------|-------------|-------------------------------------------------------------|------|---------|---|
| IGHG3 | X81695 | 147120 | 3W4         | VH-D-JH-Hinge-CH2-CH3<br>region                             | 828  | 829C>T  | 3 |
| IGHG3 | X81695 | 147120 | GEN-<br>3W4 | H.sapiens rearranged IgG<br>VH-D-JH-Hinge-CH2-CH3<br>region | 842  | 843C>T  | 3 |
| IGHG3 | X81695 | 147120 | GEN-<br>3W4 | H.sapiens rearranged IgG<br>VH-D-JH-Hinge-CH2-CH3<br>region | 849  | 850G>T  | 3 |
| IGHG3 | X81695 | 147120 | GEN-<br>3W4 | H.sapiens rearranged IgG<br>VH-D-JH-Hinge-CH2-CH3<br>region | 853  | 854A>C  | 3 |
| IGHG3 | X81695 | 147120 | GEN-<br>3W4 | H.sapiens rearranged IgG<br>VH-D-JH-Hinge-CH2-CH3<br>region | 900  | 901T>C  | 3 |
| IGHG3 | X81695 | 147120 | GEN-<br>3W4 | H.sapiens rearranged IgG<br>VH-D-JH-Hinge-CH2-CH3<br>region | 905  | 906G>A  | 3 |
| IGHG3 | X81695 | 147120 | GEN-<br>3W4 | H.sapiens rearranged IgG<br>VH-D-JH-Hinge-CH2-CH3<br>region | 916  | 917G>A  | 3 |
| IGHG3 | X81695 | 147120 | GEN-<br>3W4 | H.sapiens rearranged IgG<br>VH-D-JH-Hinge-CH2-CH3<br>region | 957  | 958G>C  | 3 |
| IGHG3 | X81695 | 147120 | GEN-<br>3W4 | H.sapiens rearranged IgG<br>VH-D-JH-Hinge-CH2-CH3<br>region | 963  | 964G>A  | 3 |
| IGHG3 | X81695 | 147120 | GEN-<br>3W4 | H.sapiens rearranged IgG<br>VH-D-JH-Hinge-CH2-CH3<br>region | 970  | 971G>A  | 3 |
| IGHG3 | X81695 | 147120 | GEN-<br>3W4 | H.sapiens rearranged IgG<br>VH-D-JH-Hinge-CH2-CH3<br>region | 973  | 974C>G  | 3 |
| IGHG3 | X81695 | 147120 | GEN-<br>3W4 | H.sapiens rearranged IgG<br>VH-D-JH-Hinge-CH2-CH3<br>region | 999  | 1000C>T | 3 |
| IGHG3 | X81695 | 147120 | GEN-<br>3W4 | H.sapiens rearranged IgG<br>VH-D-JH-Hinge-CH2-CH3<br>region | 1002 | 1003T>C | 3 |

|        |        |        |         |                                                       |      |         |       |
|--------|--------|--------|---------|-------------------------------------------------------|------|---------|-------|
| IGHG3  | X81695 | 147120 | GEN-3W4 | H.sapiens rearranged IgG VH-D-JH-Hinge-CH2-CH3 region | 1012 | 1013A>C | 3     |
| IGHG3  | X81695 | 147120 | GEN-3W4 | H.sapiens rearranged IgG VH-D-JH-Hinge-CH2-CH3 region | 1045 | 1046G>A | 3     |
| IGHG3  | X81695 | 147120 | GEN-3W4 | H.sapiens rearranged IgG VH-D-JH-Hinge-CH2-CH3 region | 1050 | 1051C>T | 3     |
| IGHG3  | X81695 | 147120 | GEN-3W4 | H.sapiens rearranged IgG VH-D-JH-Hinge-CH2-CH3 region | 1073 | 1074C>G | 3     |
| IGHG3  | X81695 | 147120 | GEN-3W4 | H.sapiens rearranged IgG VH-D-JH-Hinge-CH2-CH3 region | 1075 | 1076C>T | 3     |
| IGHG3  | X81695 | 147120 | GEN-3W4 | H.sapiens rearranged IgG VH-D-JH-Hinge-CH2-CH3 region | 1088 | 1089A>T | 3     |
| IGHG3  | X81695 | 147120 | GEN-3W4 | H.sapiens rearranged IgG VH-D-JH-Hinge-CH2-CH3 region | 1092 | 1093G>A | 3     |
| IGHG3  | X81695 | 147120 | GEN-3W4 | H.sapiens rearranged IgG VH-D-JH-Hinge-CH2-CH3 region | 1113 | 1114C>T | 3     |
| IGHG3  | X81695 | 147120 | GEN-3W4 | H.sapiens rearranged IgG VH-D-JH-Hinge-CH2-CH3 region | 1130 | 1131G>C | 3     |
| IGHG3  | X81695 | 147120 | GEN-3W4 | H.sapiens rearranged IgG VH-D-JH-Hinge-CH2-CH3 region | 1137 | 1138G>A | 3     |
| X82321 | X82321 | None   | GEN-3WT | H.sapiens mRNA for thiol-specific antioxidant         | 304  | 304G>A  | G102R |
| X82321 | X82321 | None   | GEN-3WT | H.sapiens mRNA for thiol-specific antioxidant         | 422  | 422G>T  | W141L |
| X82321 | X82321 | None   | GEN-3WT | H.sapiens mRNA for thiol-specific antioxidant         | 640  | 640C>G  | 3     |
| X82321 | X82321 | None   | GEN-3WT | H.sapiens mRNA for thiol-specific antioxidant         | 655  | 655C>T  | 3     |
| HLA-C  | X83394 | 142840 | GEN-3XX | H.sapiens mRNA for HLA-Cw*0704                        | 43   | 22G>A   | A8T   |
| HLA-C  | X83394 | 142840 | GEN-    | H.sapiens mRNA for HLA-                               | 49   | 28C>A   | L10I  |

|       |        |        |                    |                                               |     |        |       |
|-------|--------|--------|--------------------|-----------------------------------------------|-----|--------|-------|
| HLA-C | X83394 | 142840 | 3XX<br>GEN-<br>3XX | Cw*0704<br>H.sapiens mRNA for HLA-<br>Cw*0704 | 68  | 47G>C  | G16A  |
| HLA-C | X83394 | 142840 | 3XX<br>GEN-<br>3XX | H.sapiens mRNA for HLA-<br>Cw*0704            | 80  | 59C>T  | T20I  |
| HLA-C | X83394 | 142840 | 3XX<br>GEN-<br>3XX | H.sapiens mRNA for HLA-<br>Cw*0704            | 94  | 73T>G  | C25G  |
| HLA-C | X83394 | 142840 | 3XX<br>GEN-<br>3XX | H.sapiens mRNA for HLA-<br>Cw*0704            | 118 | 97G>T  | D33Y  |
| HLA-C | X83394 | 142840 | 3XX<br>GEN-<br>3XX | H.sapiens mRNA for HLA-<br>Cw*0704            | 126 | 105C>T | S     |
| HLA-C | X83394 | 142840 | 3XX<br>GEN-<br>3XX | H.sapiens mRNA for HLA-<br>Cw*0704            | 155 | 134G>A | R45H  |
| HLA-C | X83394 | 142840 | 3XX<br>GEN-<br>3XX | H.sapiens mRNA for HLA-<br>Cw*0704            | 163 | 142T>G | S48A  |
| HLA-C | X83394 | 142840 | 3XX<br>GEN-<br>3XX | H.sapiens mRNA for HLA-<br>Cw*0704            | 222 | 201G>A | S     |
| HLA-C | X83394 | 142840 | 3XX<br>GEN-<br>3XX | H.sapiens mRNA for HLA-<br>Cw*0704            | 234 | 213C>G | S     |
| HLA-C | X83394 | 142840 | 3XX<br>GEN-<br>3XX | H.sapiens mRNA for HLA-<br>Cw*0704            | 239 | 218C>A | A73E  |
| HLA-C | X83394 | 142840 | 3XX<br>GEN-<br>3XX | H.sapiens mRNA for HLA-<br>Cw*0704            | 291 | 270G>C | K90N  |
| HLA-C | X83394 | 142840 | 3XX<br>GEN-<br>3XX | H.sapiens mRNA for HLA-<br>Cw*0704            | 310 | 289G>A | A97T  |
| HLA-C | X83394 | 142840 | 3XX<br>GEN-<br>3XX | H.sapiens mRNA for HLA-<br>Cw*0704            | 323 | 302G>A | S101N |
| HLA-C | X83394 | 142840 | 3XX<br>GEN-<br>3XX | H.sapiens mRNA for HLA-<br>Cw*0704            | 333 | 312C>A | N104K |
| HLA-C | X83394 | 142840 | 3XX<br>GEN-<br>3XX | H.sapiens mRNA for HLA-<br>Cw*0704            | 362 | 341A>C | D114A |
| HLA-C | X83394 | 142840 | 3XX<br>GEN-<br>3XX | H.sapiens mRNA for HLA-<br>Cw*0704            | 374 | 353C>T | T118I |
| HLA-C | X83394 | 142840 | 3XX<br>GEN-<br>3XX | H.sapiens mRNA for HLA-<br>Cw*0704            | 382 | 361A>T | R121W |
| HLA-C | X83394 | 142840 | 3XX<br>GEN-<br>3XX | H.sapiens mRNA for HLA-<br>Cw*0704            | 408 | 387C>G | S     |
| HLA-C | X83394 | 142840 | 3XX<br>GEN-<br>3XX | H.sapiens mRNA for HLA-<br>Cw*0704            | 430 | 409T>C | Y137H |
| HLA-C | X83394 | 142840 | 3XX<br>GEN-<br>3XX | H.sapiens mRNA for HLA-<br>Cw*0704            | 433 | 412G>A | D138N |

|       |        |        |             |                                    |     |        |       |
|-------|--------|--------|-------------|------------------------------------|-----|--------|-------|
| HLA-C | X83394 | 142840 | GEN-<br>3XX | H.sapiens mRNA for HLA-<br>Cw*0704 | 441 | 420C>A | F140L |
| HLA-C | X83394 | 142840 | GEN-<br>3XX | H.sapiens mRNA for HLA-<br>Cw*0704 | 474 | 453C>T | S     |
| HLA-C | X83394 | 142840 | GEN-<br>3XX | H.sapiens mRNA for HLA-<br>Cw*0704 | 480 | 459C>T | S     |
| HLA-C | X83394 | 142840 | GEN-<br>3XX | H.sapiens mRNA for HLA-<br>Cw*0704 | 495 | 474C>T | S     |
| HLA-C | X83394 | 142840 | GEN-<br>3XX | H.sapiens mRNA for HLA-<br>Cw*0704 | 507 | 486C>G | S     |
| HLA-C | X83394 | 142840 | GEN-<br>3XX | H.sapiens mRNA for HLA-<br>Cw*0704 | 520 | 499A>T | T167S |
| HLA-C | X83394 | 142840 | GEN-<br>3XX | H.sapiens mRNA for HLA-<br>Cw*0704 | 533 | 512T>G | L171W |
| HLA-C | X83394 | 142840 | GEN-<br>3XX | H.sapiens mRNA for HLA-<br>Cw*0704 | 548 | 527C>A | A176E |
| HLA-C | X83394 | 142840 | GEN-<br>3XX | H.sapiens mRNA for HLA-<br>Cw*0704 | 622 | 601A>G | K201E |
| HLA-C | X83394 | 142840 | GEN-<br>3XX | H.sapiens mRNA for HLA-<br>Cw*0704 | 626 | 605C>A | T202K |
| HLA-C | X83394 | 142840 | GEN-<br>3XX | H.sapiens mRNA for HLA-<br>Cw*0704 | 639 | 618G>A | S     |
| HLA-C | X83394 | 142840 | GEN-<br>3XX | H.sapiens mRNA for HLA-<br>Cw*0704 | 644 | 623C>A | P208H |
| HLA-C | X83394 | 142840 | GEN-<br>3XX | H.sapiens mRNA for HLA-<br>Cw*0704 | 669 | 648C>T | S     |
| HLA-C | X83394 | 142840 | GEN-<br>3XX | H.sapiens mRNA for HLA-<br>Cw*0704 | 673 | 652C>G | L218V |
| HLA-C | X83394 | 142840 | GEN-<br>3XX | H.sapiens mRNA for HLA-<br>Cw*0704 | 724 | 703G>A | A235T |
| HLA-C | X83394 | 142840 | GEN-<br>3XX | H.sapiens mRNA for HLA-<br>Cw*0704 | 748 | 727C>T | R243W |
| HLA-C | X83394 | 142840 | GEN-<br>3XX | H.sapiens mRNA for HLA-<br>Cw*0704 | 756 | 735G>C | S     |
| HLA-C | X83394 | 142840 | GEN-<br>3XX | H.sapiens mRNA for HLA-<br>Cw*0704 | 765 | 744G>A | S     |
| HLA-C | X83394 | 142840 | GEN-<br>3XX | H.sapiens mRNA for HLA-<br>Cw*0704 | 768 | 747C>T | S     |
| HLA-C | X83394 | 142840 | GEN-<br>3XX | H.sapiens mRNA for HLA-<br>Cw*0704 | 777 | 756C>T | S     |
| HLA-C | X83394 | 142840 | GEN-<br>3XX | H.sapiens mRNA for HLA-<br>Cw*0704 | 835 | 814G>A | V272M |

|        |        |        |                    |                                                                       |      |           |       |
|--------|--------|--------|--------------------|-----------------------------------------------------------------------|------|-----------|-------|
| HLA-C  | X83394 | 142840 | 3XX<br>GEN-<br>3XX | Cw*0704<br>H.sapiens mRNA for HLA-<br>Cw*0704                         | 850  | 829C>G    | Q277E |
| HLA-C  | X83394 | 142840 | 3XX<br>GEN-<br>3XX | H.sapiens mRNA for HLA-<br>Cw*0704                                    | 874  | 853A>G    | M285V |
| HLA-C  | X83394 | 142840 | 3XX<br>GEN-<br>3XX | H.sapiens mRNA for HLA-<br>Cw*0704                                    | 893  | 872A>C    | Q291P |
| HLA-C  | X83394 | 142840 | 3XX<br>GEN-<br>3XX | H.sapiens mRNA for HLA-<br>Cw*0704                                    | 912  | 891C>A    | S297R |
| HLA-C  | X83394 | 142840 | 3XX<br>GEN-<br>3XX | H.sapiens mRNA for HLA-<br>Cw*0704                                    | 933  | 912C>T    | S     |
| HLA-C  | X83394 | 142840 | 3XX<br>GEN-<br>3XX | H.sapiens mRNA for HLA-<br>Cw*0704                                    | 946  | 925A>G    | M309V |
| HLA-C  | X83394 | 142840 | 3XX<br>GEN-<br>3XX | H.sapiens mRNA for HLA-<br>Cw*0704                                    | 977  | 956T>C    | V319A |
| HLA-C  | X83394 | 142840 | 3XX<br>GEN-<br>3XX | H.sapiens mRNA for HLA-<br>Cw*0704                                    | 1012 | 991A>G    | M331V |
| HLA-C  | X83394 | 142840 | 3XX<br>GEN-<br>3XX | H.sapiens mRNA for HLA-<br>Cw*0704                                    | 1070 | 1049G>C   | C350S |
| HLA-C  | X83394 | 142840 | 3XX<br>GEN-<br>3XX | H.sapiens mRNA for HLA-<br>Cw*0704                                    | 1108 | 1087A>G   | T363A |
| X83861 | X83861 | 176806 | 3XX<br>GEN-5H      | Prostaglandin E receptor 3<br>(subtype EP3) {alternative<br>products} | 387  | 180C>G    | S     |
| X84213 | X84213 | 600516 | GEN-<br>3ZC        | H.sapiens BAK mRNA for<br>BCI-2 homologue                             | 32   | (-161)C>T | 5     |
| X84213 | X84213 | 600516 | GEN-<br>3ZC        | H.sapiens BAK mRNA for<br>BCI-2 homologue                             | 317  | 125G>A    | R42H  |
| X84213 | X84213 | 600516 | GEN-<br>3ZC        | H.sapiens BAK mRNA for<br>BCI-2 homologue                             | 435  | 243C>T    | S     |
| X84213 | X84213 | 600516 | GEN-<br>3ZC        | H.sapiens BAK mRNA for<br>BCI-2 homologue                             | 616  | 424G>A    | V142I |
| X84213 | X84213 | 600516 | GEN-<br>3ZC        | H.sapiens BAK mRNA for<br>BCI-2 homologue                             | 663  | 471C>T    | S     |
| X84213 | X84213 | 600516 | GEN-<br>3ZC        | H.sapiens BAK mRNA for<br>BCI-2 homologue                             | 900  | 708T>C    | 3     |
| X84213 | X84213 | 600516 | GEN-<br>3ZC        | H.sapiens BAK mRNA for<br>BCI-2 homologue                             | 974  | 782C>T    | 3     |
| CD97   | X84700 | 601211 | GEN-<br>3ZO        | H.sapiens mRNA for<br>leucocyte antigen CD97                          | 828  | 758C>G    | P253R |
| X86474 | X86474 | 600250 | GEN-               | H.sapiens mRNA for ATAC                                               | 249  | 225A>G    | S     |

|        |        |        |               |                                                           |      |           |        |
|--------|--------|--------|---------------|-----------------------------------------------------------|------|-----------|--------|
| X86474 | X86474 | 600250 | 40W<br>GEN-   | H.sapiens mRNA for ATAC protein                           | 357  | 333T>C    | S      |
| X86474 | X86474 | 600250 | 40W<br>GEN-   | H.sapiens mRNA for ATAC protein                           | 423  | 399G>C    | 3      |
| X86474 | X86474 | 600250 | 40W<br>GEN-   | H.sapiens mRNA for ATAC protein                           | 446  | 422G>A    | 3      |
| X86681 | X86681 | 602110 | 40W<br>GEN-   | H.sapiens mRNA for ATAC protein                           | 1725 | 1340G>A   | 3      |
| X97058 | X97058 | 602451 | 41E<br>GEN-   | H.sapiens mRNA for nucleolar protein, HNP36               | 121  | (-156)T>G | 5      |
| X97370 | X97370 | 601459 | 4BB<br>GEN-   | H.sapiens mRNA for prepronociceptin                       | 167  | 144T>C    | S      |
| X97370 | X97370 | 601459 | 4BM<br>GEN-   | H.sapiens mRNA for prepronociceptin                       | 637  | 614C>A    | 3      |
| X97370 | X97370 | 601459 | 4BM<br>GEN-   | H.sapiens mRNA for prepronociceptin                       | 862  | 839C>G    | 3      |
| Y00052 | Y00052 | 123840 | 4BM<br>GEN-SX | H.sapiens mRNA for prepronociceptin                       | 221  | 207C>G    | S      |
| Y00052 | Y00052 | 123840 | GEN-SX        | Cyclophilin A                                             | 268  | 254A>G    | D85G   |
| Y00052 | Y00052 | 123840 | GEN-SX        | Cyclophilin A                                             | 332  | 318C>T    | S      |
| Y00052 | Y00052 | 123840 | GEN-SX        | Cyclophilin A                                             | 627  | 613C>A    | 3      |
| PTPRC  | Y00062 | 151460 | GEN-SY        | Human mRNA for T200 leukocyte common antigen              | 3437 | 3291T>C   | S      |
| PTPRC  | Y00062 | 151460 | GEN-SY        | Human mRNA for T200 leukocyte common antigen (CD45, LC-A) | 3441 | 3295G>A   | V1099I |
| Y00486 | Y00486 | 102600 | GEN-MGW       | Human APRT gene for adenine                               | 503  | 432C>A    | S      |
| Y00486 | Y00486 | 102600 | GEN-MGW       | phosphoribosyltransferase Human APRT gene for adenine     | 505  | 434G>C    | R145P  |
| Y00486 | Y00486 | 102600 | GEN-MGW       | phosphoribosyltransferase Human APRT gene for adenine     | 792  | 721A>G    | 3      |
| Y00749 | Y00749 | 131240 | GEN-P7        | phosphoribosyltransferase Endothelin 1                    | 846  | 594G>T    | K198N  |
| TCRG   | Y00790 | 186970 | GEN-UC        | Human mRNA for T-cell receptor gamma-chain                | 492  | 456G>A    | S      |
| TCRG   | Y00790 | 186970 | GEN-UC        | Human mRNA for T-cell                                     | 507  | 471A>G    | S      |



|        |        |        |         |                                                                                  |      |         |       |
|--------|--------|--------|---------|----------------------------------------------------------------------------------|------|---------|-------|
| TCRG   | Y00790 | 186970 | GEN-UC  | receptor gamma-chain<br>Human mRNA for T-cell                                    | 528  | 492C>T  | S     |
| TCRG   | Y00790 | 186970 | GEN-UC  | receptor gamma-chain<br>Human mRNA for T-cell                                    | 555  | 519A>T  | S     |
| TCRG   | Y00790 | 186970 | GEN-UC  | receptor gamma-chain<br>Human mRNA for T-cell                                    | 559  | 523A>G  | I175V |
| TCRG   | Y00790 | 186970 | GEN-UC  | receptor gamma-chain<br>Human mRNA for T-cell                                    | 636  | 600C>T  | S     |
| TCRG   | Y00790 | 186970 | GEN-UC  | receptor gamma-chain<br>Human mRNA for T-cell                                    | 676  | 640G>A  | E214K |
| TCRG   | Y00790 | 186970 | GEN-UC  | receptor gamma-chain<br>Human mRNA for T-cell                                    | 733  | 697A>G  | I233V |
| TCRG   | Y00790 | 186970 | GEN-UC  | receptor gamma-chain<br>Human mRNA for T-cell                                    | 849  | 813G>T  | W271C |
| TCRG   | Y00790 | 186970 | GEN-UC  | receptor gamma-chain<br>Human mRNA for T-cell                                    | 908  | 872C>T  | T291M |
| TCRG   | Y00790 | 186970 | GEN-UC  | receptor gamma-chain<br>Human mRNA for T-cell                                    | 970  | 934A>G  | R312G |
| Y00796 | Y00796 | 153370 | GEN-2B  | receptor gamma-chain<br>Leukocyte integrin alpha-I                               | 1006 | 918C>T  | S     |
| Y00796 | Y00796 | 153370 | GEN-2B  | receptor gamma-chain<br>Leukocyte integrin alpha-I                               | 4519 | 4431A>G | 3     |
| CR1    | Y00816 | 120620 | GEN-UG  | Human mRNA for<br>complement receptor type<br>1 (CR1, C3b/C4b receptor,<br>CD35) | 207  | 180G>C  | E60D  |
| Y07683 | Y07683 | 600843 | GEN-4F1 | H.sapiens mRNA for P2X3<br>purinoceptor                                          | 717  | 552C>T  | S     |
| Y07683 | Y07683 | 600843 | GEN-4F1 | H.sapiens mRNA for P2X3<br>purinoceptor                                          | 753  | 588A>G  | S     |
| Y09561 | Y09561 | None   | GEN-4F4 | H.sapiens mRNA for P2X7<br>receptor                                              | 835  | 809A>G  | H270R |
| Y09561 | Y09561 | None   | GEN-4F4 | H.sapiens mRNA for P2X7<br>receptor                                              | 946  | 920G>A  | R307Q |
| Y09561 | Y09561 | None   | GEN-4F4 | H.sapiens mRNA for P2X7<br>receptor                                              | 1068 | 1042G>A | A348T |
| Y09561 | Y09561 | None   | GEN-4F4 | H.sapiens mRNA for P2X7<br>receptor                                              | 1096 | 1070C>G | T357S |
| Y09561 | Y09561 | None   | GEN-4F4 | H.sapiens mRNA for P2X7<br>receptor                                              | 1405 | 1379A>G | Q460R |
| Y09561 | Y09561 | None   | GEN-4F4 | H.sapiens mRNA for P2X7<br>receptor                                              | 1589 | 1563C>G | H521Q |

|        |        |        |         |                                                                |      |         |       |
|--------|--------|--------|---------|----------------------------------------------------------------|------|---------|-------|
| Y09561 | Y09561 | None   | GEN-4F4 | H.sapiens mRNA for P2X7 receptor                               | 1590 | 1564G>A | V522I |
| Y09561 | Y09561 | None   | GEN-4F4 | H.sapiens mRNA for P2X7 receptor                               | 1628 | 1602G>T | S     |
| Y09561 | Y09561 | None   | GEN-4F4 | H.sapiens mRNA for P2X7 receptor                               | 1759 | 1733G>A | R578Q |
| Y09561 | Y09561 | None   | GEN-4F4 | H.sapiens mRNA for P2X7 receptor                               | 1772 | 1746G>A | S     |
| Y10659 | Y10659 | 300119 | GEN-1J6 | H.sapiens IL-13Ra mRNA                                         | 1116 | 1073G>A | G358D |
| Y12509 | Y12509 | None   | GEN-1ME | Homo sapiens mRNA for UDP-Gal:GlcNAc galactosyltransferase     | 257  | 257G>A  | G86D  |
| Y12510 | Y12510 | None   | GEN-1MC | Homo sapiens mRNA for UDPGal:GlcNAc b1,4 galactosyltransferase | 909  | 909C>T  | S     |
| Z11695 | Z11695 | 176948 | GEN-1L1 | H.sapiens 40 kDa protein kinase related to rat ERK2            | 1287 | 1153G>A | 3     |
| Z11696 | Z11696 | 601795 | GEN-1L0 | H.sapiens 44kDa protein kinase related to rat ERK1             | 449  | 449T>G  | I150S |
| Z15108 | Z15108 | 176982 | GEN-1TE | H.sapiens mRNA for protein kinase C zeta                       | 246  | 240T>C  | S     |
| Z15108 | Z15108 | 176982 | GEN-1TE | H.sapiens mRNA for protein kinase C zeta                       | 1694 | 1688A>C | D563A |
| Z15108 | Z15108 | 176982 | GEN-1TE | H.sapiens mRNA for protein kinase C zeta                       | 2033 | 2027G>A | 3     |
| Z15108 | Z15108 | 176982 | GEN-1TE | H.sapiens mRNA for protein kinase C zeta                       | 2086 | 2080T>G | 3     |
| Z22651 | Z22651 | None   | GEN-268 | H.sapiens HLA-B35 mRNA                                         | 25   | 25G>C   | V9L   |
| Z22651 | Z22651 | None   | GEN-268 | H.sapiens HLA-B35 mRNA                                         | 103  | 103G>T  | A35S  |
| Z22651 | Z22651 | None   | GEN-268 | H.sapiens HLA-B35 mRNA                                         | 106  | 106A>G  | M36V  |
| Z22651 | Z22651 | None   | GEN-268 | H.sapiens HLA-B35 mRNA                                         | 165  | 165C>G  | S     |
| Z22651 | Z22651 | None   | GEN-268 | H.sapiens HLA-B35 mRNA                                         | 209  | 209A>C  | E70A  |
| Z22651 | Z22651 | None   | GEN-268 | H.sapiens HLA-B35 mRNA                                         | 213  | 213C>G  | S     |
| Z22651 | Z22651 | None   | GEN-268 | H.sapiens HLA-B35 mRNA                                         | 222  | 222A>G  | S     |
| Z22651 | Z22651 | None   | GEN-268 | H.sapiens HLA-B35 mRNA                                         | 259  | 259A>G  | N87D  |
| Z22651 | Z22651 | None   | GEN-268 | H.sapiens HLA-B35 mRNA                                         | 261  | 261C>G  | N87K  |
| Z22651 | Z22651 | None   | GEN-268 | H.sapiens HLA-B35 mRNA                                         | 353  | 353T>C  | I118T |
| Z22651 | Z22651 | None   | GEN-268 | H.sapiens HLA-B35 mRNA                                         | 355  | 355A>C  | I119L |
| Z22651 | Z22651 | None   | GEN-268 | H.sapiens HLA-B35 mRNA                                         | 362  | 362G>C  | R121T |

|        |        |      |         |                         |      |         |       |
|--------|--------|------|---------|-------------------------|------|---------|-------|
| Z22651 | Z22651 | None | GEN-268 | H.sapiens HLA-B*35 mRNA | 379  | 379C>G  | L127V |
| Z22651 | Z22651 | None | GEN-268 | H.sapiens HLA-B*35 mRNA | 387  | 387C>G  | S     |
| Z22651 | Z22651 | None | GEN-268 | H.sapiens HLA-B*35 mRNA | 409  | 409C>T  | H137Y |
| Z22651 | Z22651 | None | GEN-268 | H.sapiens HLA-B*35 mRNA | 412  | 412G>A  | D138N |
| Z22651 | Z22651 | None | GEN-268 | H.sapiens HLA-B*35 mRNA | 435  | 435G>A  | S     |
| Z22651 | Z22651 | None | GEN-268 | H.sapiens HLA-B*35 mRNA | 463  | 463A>C  | S155R |
| Z22651 | Z22651 | None | GEN-268 | H.sapiens HLA-B*35 mRNA | 477  | 477G>C  | S     |
| Z22651 | Z22651 | None | GEN-268 | H.sapiens HLA-B*35 mRNA | 486  | 486C>G  | S     |
| Z22651 | Z22651 | None | GEN-268 | H.sapiens HLA-B*35 mRNA | 527  | 527T>A  | V176E |
| Z22651 | Z22651 | None | GEN-268 | H.sapiens HLA-B*35 mRNA | 538  | 538C>T  | R180W |
| Z22651 | Z22651 | None | GEN-268 | H.sapiens HLA-B*35 mRNA | 539  | 539G>T  | R180L |
| Z22651 | Z22651 | None | GEN-268 | H.sapiens HLA-B*35 mRNA | 544  | 544G>A  | A182T |
| Z22651 | Z22651 | None | GEN-268 | H.sapiens HLA-B*35 mRNA | 572  | 572G>C  | W191S |
| Z22651 | Z22651 | None | GEN-268 | H.sapiens HLA-B*35 mRNA | 583  | 583T>C  | Y195H |
| Z22651 | Z22651 | None | GEN-268 | H.sapiens HLA-B*35 mRNA | 603  | 603G>C  | E201D |
| Z22651 | Z22651 | None | GEN-268 | H.sapiens HLA-B*35 mRNA | 610  | 610C>G  | Q204E |
| Z22651 | Z22651 | None | GEN-268 | H.sapiens HLA-B*35 mRNA | 621  | 621C>A  | D207E |
| Z22651 | Z22651 | None | GEN-268 | H.sapiens HLA-B*35 mRNA | 623  | 623C>A  | P208H |
| Z22651 | Z22651 | None | GEN-268 | H.sapiens HLA-B*35 mRNA | 636  | 636C>T  | S     |
| Z22651 | Z22651 | None | GEN-268 | H.sapiens HLA-B*35 mRNA | 648  | 648C>T  | S     |
| Z22651 | Z22651 | None | GEN-268 | H.sapiens HLA-B*35 mRNA | 652  | 652G>A  | V218I |
| Z22651 | Z22651 | None | GEN-268 | H.sapiens HLA-B*35 mRNA | 668  | 668C>T  | A223V |
| Z22651 | Z22651 | None | GEN-268 | H.sapiens HLA-B*35 mRNA | 693  | 693C>T  | S     |
| Z22651 | Z22651 | None | GEN-268 | H.sapiens HLA-B*35 mRNA | 756  | 756T>C  | S     |
| Z22651 | Z22651 | None | GEN-268 | H.sapiens HLA-B*35 mRNA | 774  | 774A>G  | S     |
| Z22651 | Z22651 | None | GEN-268 | H.sapiens HLA-B*35 mRNA | 786  | 786T>C  | S     |
| Z22651 | Z22651 | None | GEN-268 | H.sapiens HLA-B*35 mRNA | 846  | 846A>G  | S     |
| Z22651 | Z22651 | None | GEN-268 | H.sapiens HLA-B*35 mRNA | 900  | 900A>G  | S     |
| Z22651 | Z22651 | None | GEN-268 | H.sapiens HLA-B*35 mRNA | 909  | 909G>A  | S     |
| Z22651 | Z22651 | None | GEN-268 | H.sapiens HLA-B*35 mRNA | 916  | 916A>G  | I306V |
| Z22651 | Z22651 | None | GEN-268 | H.sapiens HLA-B*35 mRNA | 985  | 985A>G  | T329A |
| Z22651 | Z22651 | None | GEN-268 | H.sapiens HLA-B*35 mRNA | 1008 | 1008C>T | S     |
| Z22651 | Z22651 | None | GEN-268 | H.sapiens HLA-B*35 mRNA | 1046 | 1046C>G | S349C |
| Z22651 | Z22651 | None | GEN-268 | H.sapiens HLA-B*35 mRNA | 1120 | 1120T>C | 3     |
| Z22651 | Z22651 | None | GEN-268 | H.sapiens HLA-B*35 mRNA | 1164 | 1164G>A | 3     |
| Z22651 | Z22651 | None | GEN-268 | H.sapiens HLA-B*35 mRNA | 1192 | 1192C>T | 3     |

|         |        |        |         |                                                                |      |         |       |
|---------|--------|--------|---------|----------------------------------------------------------------|------|---------|-------|
| Z22651  | Z22651 | None   | GEN-268 | H.sapiens HLA-B35 mRNA                                         | 1209 | 1209C>T | 3     |
| Z22651  | Z22651 | None   | GEN-268 | H.sapiens HLA-B35 mRNA                                         | 1219 | 1219C>A | 3     |
| Z22651  | Z22651 | None   | GEN-268 | H.sapiens HLA-B35 mRNA                                         | 1163 | 1135G>A | V379I |
| TAP2    | Z22935 | 170261 | GEN-26P | H.sapiens TAP2B mRNA, complete CDS                             | 1186 | 1158G>T | S     |
| TAP2    | Z22935 | 170261 | GEN-26P | H.sapiens TAP2B mRNA, complete CDS                             | 1840 | 1812G>A | S     |
| TAP2    | Z22935 | 170261 | GEN-26P | H.sapiens TAP2B mRNA, complete CDS                             | 2021 | 1993G>A | A665T |
| TAP2    | Z22935 | 170261 | GEN-26P | H.sapiens TAP2B mRNA, complete CDS                             | 2087 | 2059C>T | F     |
| TAP2    | Z22935 | 170261 | GEN-26P | H.sapiens TAP2B mRNA, complete CDS                             | 2119 | 2091T>G | S     |
| HLA-DMB | Z23139 | 142856 | GEN-277 | H.sapiens RING7 mRNA for HLA class II alpha chain-like product | 380  | 212G>A  | S71N  |
| HLA-DMB | Z23139 | 142856 | GEN-277 | H.sapiens RING7 mRNA for HLA class II alpha chain-like product | 1125 | 957C>T  | 3     |
| Z26649  | Z26649 | 600230 | GEN-2B5 | Phospholipase C beta-3                                         | 437  | 438C>T  | 3     |
| Z26649  | Z26649 | 600230 | GEN-2B5 | Phospholipase C beta-3                                         | 466  | 467G>A  | 3     |
| Z26649  | Z26649 | 600230 | GEN-2B5 | Phospholipase C beta-3                                         | 2664 | 2665C>T | 3     |
| Z26649  | Z26649 | 600230 | GEN-2B5 | Phospholipase C beta-3                                         | 3168 | 3169G>T | 3     |
| ECE1    | Z35307 | 600423 | GEN-2MA | Endothelin Converting Enzyme 1                                 | 1141 | 1104C>T | S     |
| ECE1    | Z35307 | 600423 | GEN-2MA | Endothelin Converting Enzyme 1                                 | 1627 | 1590T>C | S     |
| ECE1    | Z35307 | 600423 | GEN-2MA | Endothelin Converting Enzyme 1                                 | 1696 | 1659G>A | S     |
| ECE1    | Z35307 | 600423 | GEN-2MA | Endothelin Converting Enzyme 1                                 | 1946 | 1909G>A | V637M |
| ECE1    | Z35307 | 600423 | GEN-2MA | Endothelin Converting Enzyme 1                                 | 2433 | 2396G>A | 3     |
| Z35491  | Z35491 | 601497 | GEN-2ME | H.sapiens mRNA for novel glucocorticoid receptor-              | 315  | 37G>A   | E13K  |

|        |        |        |         |                                                                     |      |         |       |
|--------|--------|--------|---------|---------------------------------------------------------------------|------|---------|-------|
| Z35491 | Z35491 | 601497 | GEN-2ME | H.sapiens mRNA for novel glucocorticoid receptor-associated protein | 333  | 55G>A   | E19K  |
| Z35491 | Z35491 | 601497 | GEN-2ME | H.sapiens mRNA for novel glucocorticoid receptor-associated protein | 1297 | 1019A>C | 3     |
| PDE4C  | Z46632 | 600128 | GEN-2X2 | H.sapiens HSPDE4C1 gene for 3,5-cyclic AMP phosphodiesterase        | 280  | 169C>T  | R57C  |
| PDE4C  | Z46632 | 600128 | GEN-2X2 | H.sapiens HSPDE4C1 gene for 3,5-cyclic AMP phosphodiesterase        | 1142 | 1031G>A | R344Q |
| Z48810 | Z48810 | 602664 | GEN-2YJ | H.sapiens mRNA for TX protease precursor                            | 1280 | 1239A>C | 3     |
| Z56281 | Z56281 | 603734 | GEN-36V | H.sapiens mRNA for interferon regulatory factor                     | 883  | 837G>A  | S     |
| Z56281 | Z56281 | 603734 | GEN-36V | H.sapiens mRNA for interferon regulatory factor                     | 1114 | 1068G>A | S     |
| Z56281 | Z56281 | 603734 | GEN-36V | H.sapiens mRNA for interferon regulatory factor                     | 1175 | 1129G>A | E377K |
| Z56281 | Z56281 | 603734 | GEN-36V | H.sapiens mRNA for interferon regulatory factor                     | 1326 | 1280G>C | S427T |
| Z56281 | Z56281 | 603734 | GEN-36V | H.sapiens mRNA for interferon regulatory factor                     | 1373 | 1327A>C | 3     |

Table 16.  
Identified  
Variances  
In Genes  
for  
Pathways  
Identified  
in  
Endocrine  
and

SD-144146.1

Metabolic  
Disease

|         |   |         |        |         |                                                                       |      |         |       |
|---------|---|---------|--------|---------|-----------------------------------------------------------------------|------|---------|-------|
| AB00026 | 3 | AB00026 | 602784 | GEN-16N | Human mRNA for prepro cortistatin like peptide, complete cds          | 215  | 210T>C  | S     |
| AB00238 | 5 | AB00238 | 601698 | GEN-1D6 | Human mRNA for KIAA0387 gene, partial cds                             | 612  | 612A>G  | S     |
| AB00238 | 5 | AB00238 | 601698 | GEN-1D6 | Human mRNA for KIAA0387 gene, partial cds                             | 628  | 628A>G  | T210A |
| AB00238 | 5 | AB00238 | 601698 | GEN-1D6 | Human mRNA for KIAA0387 gene, partial cds                             | 871  | 871T>C  | +291Q |
| AB00238 | 5 | AB00238 | 601698 | GEN-1D6 | Human mRNA for KIAA0387 gene, partial cds                             | 948  | 948G>A  | S     |
| AB00238 | 5 | AB00238 | 601698 | GEN-1D6 | Human mRNA for KIAA0387 gene, partial cds                             | 973  | 973T>C  | +325R |
| AB00238 | 5 | AB00238 | 601698 | GEN-1D6 | Human mRNA for KIAA0387 gene, partial cds                             | 1600 | 1600C>T | R534C |
| AB00238 | 5 | AB00238 | 601698 | GEN-1D6 | Human mRNA for KIAA0387 gene, partial cds                             | 2308 | 2308T>C | C770R |
| AB00238 | 5 | AB00238 | 601698 | GEN-1D6 | Human mRNA for KIAA0387 gene, partial cds                             | 2770 | 2770G>A | V924M |
| AB00238 | 5 | AB00238 | 601698 | GEN-1D6 | Human mRNA for KIAA0387 gene, partial cds                             | 3727 | 3727G>A | 3     |
| AB00238 | 5 | AB00238 | 601698 | GEN-1D6 | Human mRNA for KIAA0387 gene, partial cds                             | 4036 | 4036G>A | 3     |
| AB00238 | 5 | AB00238 | 601698 | GEN-1D6 | Human mRNA for KIAA0387 gene, partial cds                             | 4602 | 4602C>A | 3     |
| AB00238 | 5 | AB00238 | 601698 | GEN-1D6 | Human mRNA for KIAA0387 gene, partial cds                             | 4621 | 4621C>A | 3     |
| AB00528 | 9 | AB00528 | 300135 | GEN-KVU | Homo sapiens mRNA for ABC transporter 7 protein, complete cds         | 2137 | 2069A>T | H690L |
| AB00529 | 3 | AB00529 | 170290 | GEN-W4  | Homo sapiens mRNA for perilipin, complete cds                         | 2197 | 2073A>T | 3     |
| AB00942 | 6 | AB00942 | 600130 | GEN-MDN | Homo sapiens gene for apobec-1                                        | 1016 | 534C>T  | S     |
| AB01071 | 0 | AB01071 | 602601 | GEN-1SQ | Homo sapiens mRNA for lectin-like oxidized LDL receptor, complete cds | 1071 | 1010T>A | 3     |
| AB01071 | 0 | AB01071 | 602601 | GEN-    | Homo sapiens mRNA for                                                 | 1073 | 1012T>C | 3     |

|          |          |         |                                                                                       |      |         |      |
|----------|----------|---------|---------------------------------------------------------------------------------------|------|---------|------|
| 0        | 0        | 1SQ     | lectin-like oxidized LDL receptor, complete cds                                       | 1073 | 1012T>C | 3    |
| AB01071  | AB01071  | GEN-1SQ | Homo sapiens mRNA for lectin-like oxidized LDL receptor, complete cds                 | 1801 | 1740A>G | 3    |
| AB01071  | AB01071  | GEN-1SQ | Homo sapiens mRNA for lectin-like oxidized LDL receptor, complete cds                 | 2199 | 2138G>A | 3    |
| AB01071  | AB01071  | GEN-1SQ | Homo sapiens mRNA for lectin-like oxidized LDL receptor, complete cds                 | 249  | 213T>C  | S    |
| AB01336  | AB01336  | GEN-L6C | Homo sapiens mRNA for DPM2, complete cds                                              | 263  | 227C>G  | T76S |
| AB01336  | AB01336  | GEN-L6C | Homo sapiens mRNA for DPM2, complete cds                                              | 2468 | 2369G>A | 3    |
| AB01678  | AB01678  | GEN-L39 | Homo sapiens mRNA for Glutamine:fructose-6-phosphate amidotransferase, complete cds   | 2549 | 2450G>A | 3    |
| AB01678  | AB01678  | GEN-L39 | Homo sapiens mRNA for Glutamine:fructose-6-phosphate amidotransferase, complete cds   | 2755 | 2656G>A | 3    |
| AB01678  | AB01678  | GEN-L39 | Homo sapiens mRNA for Glutamine:fructose-6-phosphate amidotransferase, complete cds   | 3998 | 3914G>T | 3    |
| ACLY     | X64330   | GEN-3F0 | H.sapiens mRNA for ATP-citrate lyase                                                  | 4229 | 4145A>C | 3    |
| ACLY     | X64330   | GEN-3F0 | H.sapiens mRNA for ATP-citrate lyase                                                  | 1044 | 1038T>C | S    |
| AF001174 | AF001174 | GEN-18T | Homo sapiens p38beta2 MAP kinase mRNA, complete cds                                   | 75   | 67T>C   | C23R |
| AF001437 | AF001437 | GEN-9T  | Dihydrolipoamide S-acetyltransferase (E2 component of pyruvate dehydrogenase complex) |      |         |      |

|          |          |        |             |                                                                                                 |      |         |       |
|----------|----------|--------|-------------|-------------------------------------------------------------------------------------------------|------|---------|-------|
| AF001437 | AF001437 | 245349 | GEN-9T      | Dihydrolipoamide S-<br>acetyltransferase (E2<br>component of pyruvate<br>dehydrogenase complex) | 116  | 108C>T  | S     |
| AF001437 | AF001437 | 245349 | GEN-9T      | Dihydrolipoamide S-<br>acetyltransferase (E2<br>component of pyruvate<br>dehydrogenase complex) | 759  | 751T>G  | S251A |
| AF001437 | AF001437 | 245349 | GEN-9T      | Dihydrolipoamide S-<br>acetyltransferase (E2<br>component of pyruvate<br>dehydrogenase complex) | 806  | 798C>T  | S     |
| AF001437 | AF001437 | 245349 | GEN-9T      | Dihydrolipoamide S-<br>acetyltransferase (E2<br>component of pyruvate<br>dehydrogenase complex) | 866  | 858T>C  | S     |
| AF001437 | AF001437 | 245349 | GEN-9T      | Dihydrolipoamide S-<br>acetyltransferase (E2<br>component of pyruvate<br>dehydrogenase complex) | 2000 | 1992G>T | 3     |
| AF001437 | AF001437 | 245349 | GEN-9T      | Dihydrolipoamide S-<br>acetyltransferase (E2<br>component of pyruvate<br>dehydrogenase complex) | 2158 | 2150C>A | 3     |
| AF004709 | AF004709 | 602899 | GEN-UX      | Homo sapiens stress-<br>activated protein kinase 4<br>mRNA, complete cds                        | 432  | 384G>A  | S     |
| AF009923 | AF009923 | 603169 | GEN-<br>KZM | Homo sapiens<br>preprocathepsin P mRNA,<br>partial cds                                          | 702  | 702C>T  | S     |
| AF009923 | AF009923 | 603169 | GEN-<br>KZM | Homo sapiens<br>preprocathepsin P mRNA,<br>partial cds                                          | 1018 | 1018T>C | 3     |
| AF009923 | AF009923 | 603169 | GEN-<br>KZM | Homo sapiens<br>preprocathepsin P mRNA,<br>partial cds                                          | 1129 | 1129G>A | 3     |
| AF013611 | AF013611 | 602364 | GEN-<br>20Z | Homo sapiens lymphopain<br>mRNA, complete cds                                                   | 537  | 537T>G  | H179Q |
| AF030625 | AF030625 | 600821 | GEN-2       | Vasopressin V1A receptor                                                                        | 314  | 291C>T  | S     |
| AF030625 | AF030625 | 600821 | GEN-2       | Vasopressin V1A receptor                                                                        | 431  | 408T>C  | S     |
| AF030625 | AF030625 | 600821 | GEN-2       | Vasopressin V1A receptor                                                                        | 506  | 483A>G  | S     |



|          |          |        |             |                                                                                                    |      |         |        |
|----------|----------|--------|-------------|----------------------------------------------------------------------------------------------------|------|---------|--------|
| AF053712 | AF053712 | None   | GEN-<br>MM2 | Homo sapiens<br>osteoprotegerin ligand<br>mRNA, complete cds                                       | 2086 | 1902T>G | 3      |
| AF064548 | AF064548 | 603506 | GEN-<br>KV4 | Homo sapiens low-density<br>lipoprotein receptor-related<br>protein 5 (LRP5) mRNA,<br>complete cds | 1695 | 1647C>T | S      |
| AF064548 | AF064548 | 603506 | GEN-<br>KV4 | Homo sapiens low-density<br>lipoprotein receptor-related<br>protein 5 (LRP5) mRNA,<br>complete cds | 4037 | 3989C>T | A1330V |
| AF064548 | AF064548 | 603506 | GEN-<br>KV4 | Homo sapiens low-density<br>lipoprotein receptor-related<br>protein 5 (LRP5) mRNA,<br>complete cds | 4683 | 4635C>A | S      |
| AF064548 | AF064548 | 603506 | GEN-<br>KV4 | Homo sapiens low-density<br>lipoprotein receptor-related<br>protein 5 (LRP5) mRNA,<br>complete cds | 4802 | 4754C>T | S1585L |
| AF066859 | AF066859 | 232600 | GEN-<br>LKT | Homo sapiens muscle<br>glycogen phosphorylase<br>(PYGM) mRNA, complete<br>cds                      | 53   | 53G>A   | G18D   |
| AF066859 | AF066859 | 232600 | GEN-<br>LKT | Homo sapiens muscle<br>glycogen phosphorylase<br>(PYGM) mRNA, complete<br>cds                      | 856  | 856T>C  | F286L  |
| AF066859 | AF066859 | 232600 | GEN-<br>LKT | Homo sapiens muscle<br>glycogen phosphorylase<br>(PYGM) mRNA, complete<br>cds                      | 1716 | 1716C>T | S      |
| AF071748 | AF071748 | None   | GEN-<br>LOZ | Homo sapiens cathepsin F<br>(CATSF) mRNA, complete<br>cds                                          | 1055 | 963C>T  | S      |
| AF071748 | AF071748 | None   | GEN-<br>LOZ | Homo sapiens cathepsin F<br>(CATSF) mRNA, complete<br>cds                                          | 1344 | 1252G>A | 3      |
| AF071748 | AF071748 | None   | GEN-<br>LOZ | Homo sapiens cathepsin F<br>(CATSF) mRNA, complete<br>cds                                          | 1513 | 1421T>C | 3      |
| AF071748 | AF071748 | None   | GEN-<br>LOZ | Homo sapiens cathepsin F<br>(CATSF) mRNA, complete<br>cds                                          | 1574 | 1482C>A | 3      |

|          |          |        |                                                                               |      |         |       |
|----------|----------|--------|-------------------------------------------------------------------------------|------|---------|-------|
| AF071748 | AF071748 | None   | LOZ (CATSF) mRNA, complete cds                                                | 1576 | 1484G>A | 3     |
|          | GEN-LOZ  |        | Homo sapiens cathepsin F (CATSF) mRNA, complete cds                           |      |         |       |
| AGL      | U84007   | 232400 | Human glycogen debranching enzyme isoform 1 (AGL) mRNA, alternatively spliced | 7309 | 6909A>G | 3     |
|          | GEN-3Z7  |        | isoform, complete cds                                                         |      |         |       |
| AGT      | K02215   | 106150 | Human angiotensinogen mRNA, complete CDS                                      | 659  | 620C>T  | T207M |
| AGT      | K02215   | 106150 | Human angiotensinogen mRNA, complete CDS                                      | 842  | 803T>C  | M268T |
| AGT      | K02215   | 106150 | Human angiotensinogen mRNA, complete CDS                                      | 1155 | 1116G>A | S     |
| AGT      | K02215   | 106150 | Human angiotensinogen mRNA, complete CDS                                      | 1476 | 1437C>A | S     |
| AGT      | K02215   | 106150 | Human angiotensinogen mRNA, complete CDS                                      | 1821 | 1782G>A | 3     |
| AGT      | K02215   | 106150 | Human angiotensinogen mRNA, complete CDS                                      | 2053 | 2014A>C | 3     |
| AJ005162 | AJ005162 | 600067 | Homo sapiens mRNA for UDP-glucuronosyltransferase                             | 1915 | 1882A>C | 3     |
|          | GEN-KVT  |        | Human apolipoprotein H mRNA, complete cds                                     |      |         |       |
| APOH     | M62839   | 138700 | Human apolipoprotein H mRNA, complete cds                                     | 500  | 461G>A  | R154H |
| APOH     | M62839   | 138700 | Human apolipoprotein H mRNA, complete cds                                     | 835  | 796G>T  | V266L |
| APOH     | M62839   | 138700 | Human apolipoprotein H mRNA, complete cds                                     | 1098 | 1059T>C | 3     |
| ARG1     | M14502   | 207800 | Human liver arginase mRNA, complete cds                                       | 800  | 744C>T  | S     |
| AVPR1B   | AF030512 | 600264 | Homo sapiens small cell vasopressin subtype 1b receptor mRNA, complete cds    | 273  | 150G>A  | S     |
|          | GEN-25X  |        | Human bone morphogenetic protein 1 (BMP-1) mRNA                               | 2224 | 2195G>A | 3     |
| BMP1     | M22488   | 112264 | Human bone morphogenetic protein 1 (BMP-1) mRNA                               |      |         |       |
| BMP4     | M22490   | 112262 | Human bone morphogenetic protein 1 (BMP-1) mRNA                               | 849  | 455T>C  | V152A |



|         |        |        |         |                                                                                         |      |         |       |
|---------|--------|--------|---------|-----------------------------------------------------------------------------------------|------|---------|-------|
| CETP    | M30185 | 118470 | GEN-2FK | Human cholesteryl ester transfer protein mRNA, complete cds                             | 1696 | 1566G>A | 3     |
| CLU     | X14723 | 185430 | GEN-1SB | Human SP-40,40 mRNA for complement-associated protein SP-40,40 alpha-1 and beta-1 chain | 131  | 84C>T   | S     |
| CLU     | X14723 | 185430 | GEN-1SB | Human SP-40,40 mRNA for complement-associated protein SP-40,40 alpha-1 and beta-1 chain | 429  | 382G>T  | V128F |
| CLU     | X14723 | 185430 | GEN-1SB | Human SP-40,40 mRNA for complement-associated protein SP-40,40 alpha-1 and beta-1 chain | 836  | 789C>T  | S     |
| CLU     | X14723 | 185430 | GEN-1SB | Human SP-40,40 mRNA for complement-associated protein SP-40,40 alpha-1 and beta-1 chain | 1234 | 1187C>T | S396L |
| CLU     | X14723 | 185430 | GEN-1SB | Human SP-40,40 mRNA for complement-associated protein SP-40,40 alpha-1 and beta-1 chain | 1372 | 1325A>T | Y442F |
| CLU     | X14723 | 185430 | GEN-1SB | Human SP-40,40 mRNA for complement-associated protein SP-40,40 alpha-1 and beta-1 chain | 1482 | 1435C>T | 3     |
| CLU     | X14723 | 185430 | GEN-1SB | Human SP-40,40 mRNA for complement-associated protein SP-40,40 alpha-1 and beta-1 chain | 1548 | 1501C>T | 3     |
| CLU     | X14723 | 185430 | GEN-1SB | Human SP-40,40 mRNA for complement-associated protein SP-40,40 alpha-1 and beta-1 chain | 1645 | 1598A>T | 3     |
| COL18A1 | L22548 | 120328 | GEN-262 | Human collagen type XVIII alpha 1 (COL18A1) mRNA, partial cds                           | 22   | 22A>G   | I8V   |
| COL18A1 | L22548 | 120328 | GEN-262 | Human collagen type XVIII alpha 1 (COL18A1) mRNA, partial cds                           | 2071 | 2071A>G | 3     |

|         |        |        |         |                                                                                 |      |         |       |
|---------|--------|--------|---------|---------------------------------------------------------------------------------|------|---------|-------|
| COL18A1 | L22548 | 120328 | GEN-262 | Human collagen type XVIII<br>alpha 1 (COL18A1) mRNA,<br>partial cds             | 2126 | 2126A>G | 3     |
| COL18A1 | L22548 | 120328 | GEN-262 | Human collagen type XVIII<br>alpha 1 (COL18A1) mRNA,<br>partial cds             | 2395 | 2395A>G | 3     |
| COL18A1 | L22548 | 120328 | GEN-262 | Human collagen type XVIII<br>alpha 1 (COL18A1) mRNA,<br>partial cds             | 3372 | 3372A>T | 3     |
| COL18A1 | L22548 | 120328 | GEN-262 | Human collagen type XVIII<br>alpha 1 (COL18A1) mRNA,<br>partial cds             | 3374 | 3374A>C | 3     |
| CRHBP   | X58022 | 122559 | GEN-38K | Human mRNA for<br>corticotropin-releasing<br>factor binding protein<br>(CRF-BP) | 987  | 941T>G  | I314S |
| CTGF    | U14750 | 121009 | GEN-1S3 | Human connective tissue<br>growth factor mRNA,<br>partial cds                   | 1878 | 1878A>C | 3     |
| CTSG    | M16117 | 116830 | GEN-1XI | Human cathepsin G<br>mRNA, complete cds                                         | 382  | 374A>G  | N125S |
| CTSL    | X12451 | 116880 | GEN-1M1 | Human mRNA for pro-<br>cathepsin L (major<br>excreted protein MEP)              | 1300 | 1012C>T | 3     |
| CYP11B2 | D13752 | 124080 | GEN-CCD | Human CYP11B2 gene for<br>steroid 18-hydroxylase,<br>complete cds               | 1600 | 1593G>A | 3     |
| CYP21   | M17252 | 201910 | GEN-201 | Human cytochrome<br>P450c21 mRNA, 3 end                                         | 224  | 224G>A  | R75H  |
| CYP21   | M17252 | 201910 | GEN-201 | Human cytochrome<br>P450c21 mRNA, 3 end                                         | 330  | 330C>T  | S     |
| CYP21   | M17252 | 201910 | GEN-201 | Human cytochrome<br>P450c21 mRNA, 3 end                                         | 745  | 745T>C  | 3     |
| D13811  | D13811 | 238310 | GEN-AA  | Glycine cleavage system:<br>Protein T                                           | 277  | 148G>T  | V50L  |
| D13811  | D13811 | 238310 | GEN-AA  | Glycine cleavage system:<br>Protein T                                           | 1073 | 944G>A  | R315K |
| D13811  | D13811 | 238310 | GEN-AA  | Glycine cleavage system:<br>Protein T                                           | 1083 | 954G>A  | S     |
| D13811  | D13811 | 238310 | GEN-AA  | Glycine cleavage system:<br>Protein T                                           | 1773 | 1644C>T | 3     |

|        |        |        |         |                                                                                        |      |         |       |
|--------|--------|--------|---------|----------------------------------------------------------------------------------------|------|---------|-------|
| D13811 | D13811 | 238310 | GEN-AA  | Protein T<br>Glycine cleavage system:<br>Protein T                                     | 2037 | 1908C>T | 3     |
| D50678 | D50678 | 602600 | GEN-30Y | Human mRNA for apolipoprotein E receptor 2, complete cds                               | 3378 | 3276G>A | 3     |
| D50678 | D50678 | 602600 | GEN-30Y | Human mRNA for apolipoprotein E receptor 2, complete cds                               | 3755 | 3653G>A | 3     |
| D50678 | D50678 | 602600 | GEN-30Y | Human mRNA for apolipoprotein E receptor 2, complete cds                               | 3949 | 3847G>C | 3     |
| D50678 | D50678 | 602600 | GEN-30Y | Human mRNA for apolipoprotein E receptor 2, complete cds                               | 4368 | 4266T>A | 3     |
| D50678 | D50678 | 602600 | GEN-30Y | Human mRNA for apolipoprotein E receptor 2, complete cds                               | 4455 | 4353G>A | 3     |
| D63480 | D63480 | 116898 | GEN-3DN | Human mRNA for KIAA0146 gene, partial cds                                              | 1728 | 1728G>A | S     |
| D82347 | D82347 | 601724 | GEN-MIP | Neurogenic differentiation 1                                                           | 804  | 695G>A  | G232D |
| D85730 | D85730 | 140559 | GEN-LR0 | Homo sapiens HSPA1L mRNA for Heat shock protein 70 testis variant, complete cds        | 2156 | 2021C>G | 3     |
| D87258 | D87258 | 602194 | GEN-42R | Homo sapiens mRNA for serin protease with IGF-binding motif, complete cds              | 150  | 102C>T  | S     |
| D87812 | D87812 | 600528 | GEN-6   | Palmitoyltransferase I (muscle) ACAT1                                                  | 2363 | 2344T>C | 3     |
| D90228 | D90228 | 203750 | GEN-46A | Human chondroitin/dermatan sulfate proteoglycan (PG40) core protein mRNA, complete cds | 547  | 471C>A  | S     |
| DCN    | M14219 | 125255 | GEN-1QX | Human chondroitin/dermatan                                                             | 1490 | 1409A>G | 3     |
| DCN    | M14219 | 125255 | GEN-1QX | Human chondroitin/dermatan                                                             | 1534 | 1453C>T | 3     |

|      |        |        |         |                                                             |                                |      |          |       |
|------|--------|--------|---------|-------------------------------------------------------------|--------------------------------|------|----------|-------|
| DRD1 | X58987 | 126449 | GEN-4EH | sulfate proteoglycan (PG40) core protein mRNA, complete cds | D1 dopaminergic receptor       | 229  | (-48)A>G | 5     |
| DRD1 | X58987 | 126449 | GEN-4EH |                                                             | D1 dopaminergic receptor       | 366  | 90G>A    | S     |
| DRD1 | X58987 | 126449 | GEN-4EH |                                                             | D1 dopaminergic receptor       | 474  | 198G>A   | S     |
| DRD1 | X58987 | 126449 | GEN-4EH |                                                             | D1 dopaminergic receptor       | 1539 | 1263G>A  | S     |
| DRD1 | X58987 | 126449 | GEN-4EH |                                                             | D1 dopaminergic receptor       | 2040 | 1764A>C  | 3     |
| DRD1 | X58987 | 126449 | GEN-4EH |                                                             | D1 dopaminergic receptor       | 2045 | 1769C>A  | 3     |
| ECE1 | Z35307 | 600423 | GEN-2MA |                                                             | Endothelin Converting Enzyme 1 | 1141 | 1104C>T  | S     |
| ECE1 | Z35307 | 600423 | GEN-2MA |                                                             | Endothelin Converting Enzyme 1 | 1627 | 1590T>C  | S     |
| ECE1 | Z35307 | 600423 | GEN-2MA |                                                             | Endothelin Converting Enzyme 1 | 1696 | 1659G>A  | S     |
| ECE1 | Z35307 | 600423 | GEN-2MA |                                                             | Endothelin Converting Enzyme 1 | 1946 | 1909G>A  | V637M |
| ECE1 | Z35307 | 600423 | GEN-2MA |                                                             | Endothelin Converting Enzyme 1 | 2433 | 2396G>A  | 3     |
| EDN2 | M65199 | 131241 | GEN-CBS |                                                             | Endothelin 2                   | 384  | 314C>T   | A105V |
| EDN2 | M65199 | 131241 | GEN-CBS |                                                             | Endothelin 2                   | 997  | 927A>G   | 3     |
| EDN2 | M65199 | 131241 | GEN-CBS |                                                             | Endothelin 2                   | 997  | 927A>G   | 3     |
| EDN3 | X52001 | 131242 | GEN-33E |                                                             | Endothelin 3                   | 1262 | 1152G>A  | 3     |
| EDN3 | X52001 | 131242 | GEN-33E |                                                             | Endothelin 3                   | 1649 | 1539C>G  | 3     |
| EDN3 | X52001 | 131242 | GEN-33E |                                                             | Endothelin 3                   | 1700 | 1590C>T  | 3     |
| EDN3 | X52001 | 131242 | GEN-33E |                                                             | Endothelin 3                   | 1742 | 1632C>T  | 3     |
| EDN3 | X52001 | 131242 | GEN-33E |                                                             | Endothelin 3                   | 1797 | 1687C>T  | 3     |

|        |        |        |         |                                                            |      |           |   |
|--------|--------|--------|---------|------------------------------------------------------------|------|-----------|---|
| EDN3   | X52001 | 131242 | GEN-33E | Endothelin 3                                               | 1914 | 1804G>C   | 3 |
| EDN3   | X52001 | 131242 | GEN-33E | Endothelin 3                                               | 2040 | 1930C>T   | 3 |
| EDNRA  | D90348 | 131243 | GEN-4DX | Endothelin Receptor Type A                                 | 1449 | 969C>T    | S |
| EDNRA  | D90348 | 131243 | GEN-4DX | Endothelin Receptor Type A                                 | 1449 | 969C>T    | S |
| EDNRA  | D90348 | 131243 | GEN-4DX | Endothelin Receptor Type A                                 | 1485 | 1005A>G   | S |
| EDNRA  | D90348 | 131243 | GEN-4DX | Endothelin Receptor Type A                                 | 1485 | 1005A>G   | S |
| EDNRA  | D90348 | 131243 | GEN-4DX | Endothelin Receptor Type A                                 | 1834 | 1354C>G   | 3 |
| EDNRA  | D90348 | 131243 | GEN-4DX | Endothelin Receptor Type A                                 | 1834 | 1354C>G   | 3 |
| EDNRA  | D90348 | 131243 | GEN-4DX | Endothelin Receptor Type A                                 | 2228 | 1748G>A   | 3 |
| EDNRA  | D90348 | 131243 | GEN-4DX | Endothelin Receptor Type A                                 | 2376 | 1896G>A   | 3 |
| EDNRA  | D90348 | 131243 | GEN-4DX | Endothelin Receptor Type A                                 | 2764 | 2284G>A   | 3 |
| EDNRA  | D90348 | 131243 | GEN-4DX | Endothelin Receptor Type A                                 | 2764 | 2284G>A   | 3 |
| EDNRA  | D90348 | 131243 | GEN-4DX | Endothelin Receptor Type A                                 | 2840 | 2360G>C   | 3 |
| EDNRA  | D90348 | 131243 | GEN-4DX | Endothelin Receptor Type A                                 | 2935 | 2455G>A   | 3 |
| EDNRA  | D90348 | 131243 | GEN-4DX | Endothelin Receptor Type A                                 | 3294 | 2814A>G   | 3 |
| EDNRB  | L06623 | 131244 | GEN-19S | Endothelin Receptor Type B                                 | 88   | (-146)A>G | 5 |
| EDNRB  | L06623 | 131244 | GEN-19S | Endothelin Receptor Type B                                 | 332  | 99C>T     | S |
| EDNRB  | L06623 | 131244 | GEN-19S | Endothelin Receptor Type B                                 | 1064 | 831G>A    | S |
| EDNRB  | L06623 | 131244 | GEN-19S | Endothelin Receptor Type B                                 | 1064 | 831G>A    | S |
| EHHADH | L07077 | 261515 | GEN-1DF | Human enoyl-CoA: hydratase 3-hydroxyacyl-CoA dehydrogenase | 1225 | 1218G>A   | S |



|        |        |        |         |                                                                                                                                                |      |           |       |
|--------|--------|--------|---------|------------------------------------------------------------------------------------------------------------------------------------------------|------|-----------|-------|
| EHHADH | L07077 | 261515 | GEN-1DF | (EHHADH) mRNA, complete cds with repeats<br>Human enoyl-CoA hydratase 3-hydroxyacyl-CoA dehydrogenase (EHHADH) mRNA, complete cds with repeats | 1823 | 1816C>A   | P606T |
| FACL1  | L09229 | 152425 | GEN-1GI | Human long-chain acyl-coenzyme A synthetase (FACL1) mRNA, complete cds                                                                         | 3026 | 2953G>A   | 3     |
| FACL1  | L09229 | 152425 | GEN-1GI | Human long-chain acyl-coenzyme A synthetase (FACL1) mRNA, complete cds                                                                         | 3083 | 3010G>A   | 3     |
| FGF7   | M60828 | 148180 | GEN-3BE | Human keratinocyte growth factor mRNA, complete cds                                                                                            | 323  | (-123)G>C | 5     |
| FGF7   | M60828 | 148180 | GEN-3BE | Human keratinocyte growth factor mRNA, complete cds                                                                                            | 1180 | 735T>C    | 3     |
| FGF7   | M60828 | 148180 | GEN-3BE | Human keratinocyte growth factor mRNA, complete cds                                                                                            | 1201 | 756A>G    | 3     |
| FGF7   | M60828 | 148180 | GEN-3BE | Human keratinocyte growth factor mRNA, complete cds                                                                                            | 1216 | 771A>G    | 3     |
| FGF7   | M60828 | 148180 | GEN-3BE | Human keratinocyte growth factor mRNA, complete cds                                                                                            | 1218 | 773G>C    | 3     |
| FGF7   | M60828 | 148180 | GEN-3BE | Human keratinocyte growth factor mRNA, complete cds                                                                                            | 1266 | 821A>C    | 3     |
| FGF7   | M60828 | 148180 | GEN-3BE | Human keratinocyte growth factor mRNA, complete cds                                                                                            | 1306 | 861C>T    | 3     |
| FGF7   | M60828 | 148180 | GEN-3BE | Human keratinocyte growth factor mRNA, complete cds                                                                                            | 1654 | 1209A>T   | 3     |
| FGF7   | M60828 | 148180 | GEN-3BE | Human keratinocyte growth factor mRNA, complete cds                                                                                            | 1657 | 1212T>C   | 3     |

|       |        |        |         |                                                                        |      |         |   |
|-------|--------|--------|---------|------------------------------------------------------------------------|------|---------|---|
| FGF7  | M60828 | 148180 | GEN-3BE | complete cds<br>Human keratinocyte growth factor mRNA,                 | 1799 | 1354A>T | 3 |
| FGF7  | M60828 | 148180 | GEN-3BE | complete cds<br>Human keratinocyte growth factor mRNA,                 | 1801 | 1356C>T | 3 |
| FGF7  | M60828 | 148180 | GEN-3BE | complete cds<br>Human keratinocyte growth factor mRNA,                 | 1867 | 1422A>G | 3 |
| FGF7  | M60828 | 148180 | GEN-3BE | complete cds<br>Human keratinocyte growth factor mRNA,                 | 1945 | 1500C>A | 3 |
| FGF7  | M60828 | 148180 | GEN-3BE | complete cds<br>Human keratinocyte growth factor mRNA,                 | 1973 | 1528G>A | 3 |
| FGF7  | M60828 | 148180 | GEN-3BE | complete cds<br>Human keratinocyte growth factor mRNA,                 | 2167 | 1722G>A | 3 |
| FGF7  | M60828 | 148180 | GEN-3BE | complete cds<br>Human keratinocyte growth factor mRNA,                 | 2186 | 1741A>G | 3 |
| FGF7  | M60828 | 148180 | GEN-3BE | complete cds<br>Human keratinocyte growth factor mRNA,                 | 2302 | 1857T>A | 3 |
| FGF7  | M60828 | 148180 | GEN-3BE | complete cds<br>Human keratinocyte growth factor mRNA,                 | 2328 | 1883G>A | 3 |
| FGF8  | U36223 | 600483 | GEN-2MX | complete cds<br>Human fibroblast growth factor 8 (FGF-8) mRNA,         | 300  | 291T>C  | S |
| FGF8  | U36223 | 600483 | GEN-2MX | complete cds<br>Human fibroblast growth factor 8 (FGF-8) mRNA,         | 645  | 636G>C  | S |
| FGF8  | U36223 | 600483 | GEN-2MX | complete cds<br>Human fibroblast growth factor 8 (FGF-8) mRNA,         | 648  | 639A>G  | S |
| FGFR1 | X51803 | 136350 | GEN-32G | complete cds<br>Human mRNA for fibroblast growth factor (FGF) receptor | 276  | 159T>G  | S |
| FGFR2 | X52832 | 176943 | GEN-341 | Human bek mRNA for                                                     | 338  | 159A>G  | S |

|       |        |        |         |                                                                  |      |          |       |
|-------|--------|--------|---------|------------------------------------------------------------------|------|----------|-------|
| FGFR2 | X52832 | 176943 | GEN-341 | fibroblast growth factor receptor-BEK                            | 2903 | 2724A>T  | 3     |
|       |        |        |         | Human bek mRNA for fibroblast growth factor receptor-BEK         |      |          |       |
| FGFR3 | M64347 | 134934 | GEN-3EX | Human novel growth factor receptor mRNA, 3 cds                   | 3108 | 3108C>A  | 3     |
| FGFR3 | M64347 | 134934 | GEN-3EX | Human novel growth factor receptor mRNA, 3 cds                   | 3715 | 3715G>A  | 3     |
| FGFR4 | X57205 | 134935 | GEN-37M | Human FGFR-4 mRNA for fibroblast growth factor receptor (FGFR-4) | 83   | 28G>A    | V10I  |
| FGFR4 | X57205 | 134935 | GEN-37M | Human FGFR-4 mRNA for fibroblast growth factor receptor (FGFR-4) | 217  | 162T>G   | S     |
| FSHR  | M65085 | 136435 | GEN-3FQ | FSH receptor                                                     | 2105 | 2039G>A  | S680N |
| GAA   | Y00839 | 232300 | GEN-UJ  | a-glucosidase                                                    | 815  | (-14)G>A | 5     |
| GAA   | Y00839 | 232300 | GEN-UJ  | a-glucosidase                                                    | 861  | 33C>T    | S     |
| GAA   | Y00839 | 232300 | GEN-UJ  | a-glucosidase                                                    | 3301 | 2473C>T  | 3     |
| GAA   | Y00839 | 232300 | GEN-UJ  | a-glucosidase                                                    | 3477 | 2649C>T  | 3     |
| GAA   | Y00839 | 232300 | GEN-UJ  | a-glucosidase                                                    | 3496 | 2668T>G  | 3     |
| GAA   | Y00839 | 232300 | GEN-UJ  | a-glucosidase                                                    | 3509 | 2681G>A  | 3     |
| GALN  | M77140 | 137035 | GEN-3PM | H.sapiens pro-galanin mRNA, 3 end                                | 339  | 339C>T   | 3     |
| GC    | M12654 | 139200 | GEN-1MN | Human serum vitamin D-binding protein (hDBP) mRNA, complete cds  | 925  | 897T>C   | S     |
| GC    | M12654 | 139200 | GEN-1MN | Human serum vitamin D-binding protein (hDBP) mRNA, complete cds  | 1324 | 1296G>T  | E432D |
| GC    | M12654 | 139200 | GEN-1MN | Human serum vitamin D-binding protein (hDBP) mRNA, complete cds  | 1335 | 1307C>A  | T436K |
| GC    | M12654 | 139200 | GEN-1MN | Human serum vitamin D-binding protein (hDBP) mRNA, complete cds  | 1362 | 1334G>A  | R445H |
| GLP1R | U01157 | 138032 | GEN-V3  | Human glucagon-like peptide-1 receptor mRNA with CA dinucleotide | 780  | 780C>A   | F260L |

|       |        |        |         |                                                                                                |      |         |       |
|-------|--------|--------|---------|------------------------------------------------------------------------------------------------|------|---------|-------|
| GLP1R | U01157 | 138032 | GEN-V3  | repeat, complete cds<br>Human glucagon-like<br>peptide-1 receptor mRNA<br>with CA dinucleotide | 780  | 780C>A  | F260L |
| GLP1R | U01157 | 138032 | GEN-V3  | repeat, complete cds<br>Human glucagon-like<br>peptide-1 receptor mRNA<br>with CA dinucleotide | 947  | 947G>C  | G316A |
| GLP1R | U01157 | 138032 | GEN-V3  | repeat, complete cds<br>Human glucagon-like<br>peptide-1 receptor mRNA<br>with CA dinucleotide | 947  | 947G>C  | G316A |
| GLP1R | U01157 | 138032 | GEN-V3  | repeat, complete cds<br>Human glucagon-like<br>peptide-1 receptor mRNA<br>with CA dinucleotide | 1200 | 1200C>A | S     |
| GLP1R | U01157 | 138032 | GEN-V3  | repeat, complete cds<br>Human glucagon-like<br>peptide-1 receptor mRNA<br>with CA dinucleotide | 1200 | 1200C>A | S     |
| GNRHR | L07949 | 138850 | GEN-1F1 | repeat, complete cds<br>Gonadotropin releasing<br>hormone agonist                              | 1371 | 1347C>A | 3     |
| GPX1  | Y00433 | 138320 | GEN-TJ  | Human mRNA for<br>glutathione peroxidase (EC<br>1.11.1.9.)                                     | 504  | 186G>A  | S     |
| GPX1  | Y00433 | 138320 | GEN-TJ  | Human mRNA for<br>glutathione peroxidase (EC<br>1.11.1.9.)                                     | 610  | 292C>G  | R98G  |
| GPX1  | Y00433 | 138320 | GEN-TJ  | Human mRNA for<br>glutathione peroxidase (EC<br>1.11.1.9.)                                     | 911  | 593C>T  | P198L |
| GPX1  | Y00433 | 138320 | GEN-TJ  | Human mRNA for<br>glutathione peroxidase (EC<br>1.11.1.9.)                                     | 1048 | 730A>C  | 3     |
| GPX1  | Y00433 | 138320 | GEN-TJ  | Human mRNA for<br>glutathione peroxidase (EC<br>1.11.1.9.)                                     | 1110 | 792A>C  | 3     |
| GPX3  | X58295 | 138321 | GEN-38S | Human GPx-3 mRNA for<br>plasma glutathione<br>peroxidase                                       | 821  | 773C>T  | 3     |

|      |        |        |         |                                                                            |      |         |       |
|------|--------|--------|---------|----------------------------------------------------------------------------|------|---------|-------|
| GPX3 | X58295 | 138321 | GEN-38S | Human GPx-3 mRNA for plasma glutathione peroxidase                         | 979  | 931G>A  | 3     |
| GPX3 | X58295 | 138321 | GEN-38S | Human GPx-3 mRNA for plasma glutathione peroxidase                         | 1187 | 1139T>G | 3     |
| GPX3 | X58295 | 138321 | GEN-38S | Human GPx-3 mRNA for plasma glutathione peroxidase                         | 1354 | 1306C>T | 3     |
| GPX3 | X58295 | 138321 | GEN-38S | Human GPx-3 mRNA for plasma glutathione peroxidase                         | 1443 | 1395C>T | 3     |
| GPX3 | X58295 | 138321 | GEN-38S | Human GPx-3 mRNA for plasma glutathione peroxidase                         | 1516 | 1468C>A | 3     |
| GPX3 | X58295 | 138321 | GEN-38S | Human GPx-3 mRNA for plasma glutathione peroxidase                         | 1581 | 1533C>T | 3     |
| GPX4 | X71973 | 138322 | GEN-3L1 | H.sapiens GPx-4 mRNA for phospholipid hydroperoxide glutathione peroxidase | 718  | 638T>C  | 3     |
| GPX4 | X71973 | 138322 | GEN-3L1 | H.sapiens GPx-4 mRNA for phospholipid hydroperoxide glutathione peroxidase | 837  | 757C>A  | 3     |
| GPX4 | X71973 | 138322 | GEN-3L1 | H.sapiens GPx-4 mRNA for phospholipid hydroperoxide glutathione peroxidase | 882  | 802A>C  | 3     |
| GSS  | U34683 | 601002 | GEN-2LF | Human glutathione synthetase mRNA, complete cds                            | 364  | 324G>A  | S     |
| GYS1 | J04501 | 138570 | GEN-14W | Human muscle glycogen synthase mRNA, complete cds                          | 567  | 407T>C  | I136T |
| GYS1 | J04501 | 138570 | GEN-14W | Human muscle glycogen synthase mRNA, complete cds                          | 2276 | 2116C>A | R706S |
| GYS1 | J04501 | 138570 | GEN-14W | Human muscle glycogen synthase mRNA, complete cds                          | 2457 | 2297A>C | 3     |

|         |        |        |         |                                                                                                          |      |         |       |
|---------|--------|--------|---------|----------------------------------------------------------------------------------------------------------|------|---------|-------|
| GYS1    | J04501 | 138570 | GEN-14W | Human muscle glycogen synthase mRNA, complete cds                                                        | 2470 | 2310C>T | 3     |
| GYS1    | J04501 | 138570 | GEN-14W | Human muscle glycogen synthase mRNA, complete cds                                                        | 3099 | 2939T>C | 3     |
| HADHA   | U04627 | 600890 | GEN-155 | Human 78 kDa gastrin-binding protein mRNA, complete cds                                                  | 1507 | 1507G>A | V503M |
| HADHB   | D16481 | 143450 | GEN-1Y5 | Human mRNA for mitochondrial 3-ketoacyl-CoA thiolase beta-subunit of trifunctional protein, complete cds | 871  | 825T>C  | S     |
| HADHB   | D16481 | 143450 | GEN-1Y5 | Human mRNA for mitochondrial 3-ketoacyl-CoA thiolase beta-subunit of trifunctional protein, complete cds | 1607 | 1561G>C | 3     |
| HADHB   | D16481 | 143450 | GEN-1Y5 | Human mRNA for mitochondrial 3-ketoacyl-CoA thiolase beta-subunit of trifunctional protein, complete cds | 1908 | 1862A>C | 3     |
| HADHB   | D16481 | 143450 | GEN-1Y5 | Human mRNA for mitochondrial 3-ketoacyl-CoA thiolase beta-subunit of trifunctional protein, complete cds | 1911 | 1865A>C | 3     |
| HGF     | X16323 | 142409 | GEN-1Y1 | Human mRNA for hepatocyte growth factor (HGF)                                                            | 5740 | 5606T>A | 3     |
| HSD17B3 | U05659 | 264300 | GEN-186 | Human 17beta-hydroxysteroid dehydrogenase type 3 mRNA, complete cds                                      | 894  | 846G>C  | S     |
| IGFBP4  | M62403 | 146733 | GEN-3CJ | Human insulin-like growth factor binding protein 4 (IGFBP4) mRNA, complete cds                           | 859  | 776G>A  | S     |

|        |        |        |         |                                                                                           |      |         |       |
|--------|--------|--------|---------|-------------------------------------------------------------------------------------------|------|---------|-------|
| IGFBP4 | M62403 | 146733 | GEN-3CJ | Human insulin-like growth factor binding protein 4 (IGFBP4) mRNA, complete cds            | 1403 | 1320G>T | 3     |
| IGFBP4 | M62403 | 146733 | GEN-3CJ | Human insulin-like growth factor binding protein 4 (IGFBP4) mRNA, complete cds            | 1443 | 1360G>A | 3     |
| IGFBP4 | M62403 | 146733 | GEN-3CJ | Human insulin-like growth factor binding protein 4 (IGFBP4) mRNA, complete cds            | 1446 | 1363G>A | 3     |
| IGFBP4 | M62403 | 146733 | GEN-3CJ | Human insulin-like growth factor binding protein 4 (IGFBP4) mRNA, complete cds            | 1485 | 1402A>T | 3     |
| IGFBP6 | M69054 | 146735 | GEN-3J0 | Human insulin-like growth factor binding protein 6 (IGFBP6) mRNA, complete mature peptide | 751  | 751A>C  | 3     |
| IGFBP6 | M69054 | 146735 | GEN-3J0 | Human insulin-like growth factor binding protein 6 (IGFBP6) mRNA, complete mature peptide | 835  | 835A>C  | 3     |
| IGFBP6 | M69054 | 146735 | GEN-3J0 | Human insulin-like growth factor binding protein 6 (IGFBP6) mRNA, complete mature peptide | 850  | 850G>A  | 3     |
| ITGA5  | X06256 | 135620 | GEN-19B | Human mRNA for fibronectin receptor alpha subunit                                         | 2562 | 2539C>A | L847I |
| J00117 | J00117 | 118860 | GEN-2H  | CHORIOGONADOTROPI N BETA CHAIN PRECURSOR                                                  | 17   | (-9)G>A | 5     |
| J00117 | J00117 | 118860 | GEN-2H  | CHORIOGONADOTROPI N BETA CHAIN PRECURSOR                                                  | 155  | 130C>A  | P44T  |
| J00117 | J00117 | 118860 | GEN-2H  | CHORIOGONADOTROPI N BETA CHAIN PRECURSOR                                                  | 331  | 306C>A  | F     |
| J00117 | J00117 | 118860 | GEN-2H  | CHORIOGONADOTROPI N BETA CHAIN PRECURSOR                                                  | 435  | 410A>C  | D137A |

|        |        |        |             |                                                                                                                                        |       |          |        |
|--------|--------|--------|-------------|----------------------------------------------------------------------------------------------------------------------------------------|-------|----------|--------|
| J00117 | J00117 | 118860 | GEN-2H      | CHORIOGONADOTROPI<br>N BETA CHAIN<br>PRECURSOR                                                                                         | 475   | 450C>T   | S      |
| J00117 | J00117 | 118860 | GEN-2H      | CHORIOGONADOTROPI<br>N BETA CHAIN<br>PRECURSOR                                                                                         | 517   | 492A>C   | S      |
| J00123 | J00123 | 131330 | GEN-<br>MK4 | Human enkephalin gene                                                                                                                  | 81    | 81C>T    | S      |
| J00277 | J00277 | 190020 | GEN-<br>MH8 | Human (genomic clones<br>lambda-[SK2-T2, HS578T];<br>cDNA clones RS-[3.4, 6])<br>c-Ha-ras1 proto-oncogene,<br>complete coding sequence | 81    | 81T>C    | S      |
| J02610 | J02610 | 107730 | GEN-6N      | Apolipoprotein B (including<br>Ag(x) antigen)                                                                                          | 1931  | 1853T>C  | V618A  |
| J02610 | J02610 | 107730 | GEN-6N      | Apolipoprotein B (including<br>Ag(x) antigen)                                                                                          | 6616  | 6538C>T  | F      |
| J02610 | J02610 | 107730 | GEN-6N      | Apolipoprotein B (including<br>Ag(x) antigen)                                                                                          | 7014  | 6936T>C  | S      |
| J02610 | J02610 | 107730 | GEN-6N      | Apolipoprotein B (including<br>Ag(x) antigen)                                                                                          | 7623  | 7545T>C  | S      |
| J02610 | J02610 | 107730 | GEN-6N      | Apolipoprotein B (including<br>Ag(x) antigen)                                                                                          | 8294  | 8216C>T  | P2739L |
| J02610 | J02610 | 107730 | GEN-6N      | Apolipoprotein B (including<br>Ag(x) antigen)                                                                                          | 8625  | 8547T>C  | S      |
| J02610 | J02610 | 107730 | GEN-6N      | Apolipoprotein B (including<br>Ag(x) antigen)                                                                                          | 10033 | 9955G>C  | D3319H |
| J02610 | J02610 | 107730 | GEN-6N      | Apolipoprotein B (including<br>Ag(x) antigen)                                                                                          | 10358 | 10280C>A | T3427K |
| J02610 | J02610 | 107730 | GEN-6N      | Apolipoprotein B (including<br>Ag(x) antigen)                                                                                          | 10372 | 10294C>G | Q3432E |
| J02610 | J02610 | 107730 | GEN-6N      | Apolipoprotein B (including<br>Ag(x) antigen)                                                                                          | 11273 | 11195T>C | I3732T |
| J02610 | J02610 | 107730 | GEN-6N      | Apolipoprotein B (including<br>Ag(x) antigen)                                                                                          | 11705 | 11627C>T | A3876V |
| J02610 | J02610 | 107730 | GEN-6N      | Apolipoprotein B (including<br>Ag(x) antigen)                                                                                          | 11862 | 11784T>A | S      |
| J02610 | J02610 | 107730 | GEN-6N      | Apolipoprotein B (including<br>Ag(x) antigen)                                                                                          | 11923 | 11845T>C | F3949L |



|        |        |        |        |                                                             |       |          |        |
|--------|--------|--------|--------|-------------------------------------------------------------|-------|----------|--------|
| J02610 | J02610 | 107730 | GEN-6N | Apolipoprotein B (including Ag(x) antigen)                  | 12461 | 12383A>T | E4128V |
| J02610 | J02610 | 107730 | GEN-6N | Apolipoprotein B (including Ag(x) antigen)                  | 12476 | 12398G>C | G4133A |
| J02610 | J02610 | 107730 | GEN-6N | Apolipoprotein B (including Ag(x) antigen)                  | 12486 | 12408G>C | S      |
| J02610 | J02610 | 107730 | GEN-6N | Apolipoprotein B (including Ag(x) antigen)                  | 12619 | 12541G>A | E4181K |
| J02611 | J02611 | 107740 | GEN-6O | Human apolipoprotein D mRNA, complete cds                   | 676   | 615T>G   | 3      |
| J02611 | J02611 | 107740 | GEN-6O | Human apolipoprotein D mRNA, complete cds                   | 683   | 622T>G   | 3      |
| J02611 | J02611 | 107740 | GEN-6O | Human apolipoprotein D mRNA, complete cds                   | 701   | 640C>G   | 3      |
| J02611 | J02611 | 107740 | GEN-6O | Human apolipoprotein D mRNA, complete cds                   | 745   | 684A>G   | 3      |
| J03209 | J03209 | 185250 | GEN-PK | Human matrix metalloproteinase-3 (MMP-3) mRNA, complete cds | 133   | 133G>A   | E45K   |
| J03209 | J03209 | 185250 | GEN-PK | Human matrix metalloproteinase-3 (MMP-3) mRNA, complete cds | 288   | 288C>T   | S      |
| J03210 | J03210 | 120360 | GEN-ZY | Human collagenase type IV mRNA, 3 end                       | 721   | 721C>T   | P241S  |
| J03210 | J03210 | 120360 | GEN-ZY | Human collagenase type IV mRNA, 3 end                       | 1759  | 1759C>T  | P587S  |
| J03242 | J03242 | 147470 | GEN-PJ | Insulin-like growth factor 2                                | 932   | 380G>A   | R127H  |
| J03242 | J03242 | 147470 | GEN-PJ | Insulin-like growth factor 2                                | 1063  | 511G>A   | A171T  |
| J03242 | J03242 | 147470 | GEN-PJ | Insulin-like growth factor 2                                | 1190  | 638C>G   | 3      |
| J03242 | J03242 | 147470 | GEN-PJ | Insulin-like growth factor 2                                | 1201  | 649C>T   | 3      |
| J03258 | J03258 | 601769 | GEN-2J | Vitamin D (1,25-dihydroxyvitamin D3) receptor               | 172   | 57C>T    | S      |
| J03258 | J03258 | 601769 | GEN-2J | Vitamin D (1,25-dihydroxyvitamin D3) receptor               | 559   | 444C>T   | S      |
| J03258 | J03258 | 601769 | GEN-2J | Vitamin D (1,25-dihydroxyvitamin D3) receptor               | 1704  | 1589C>A  | 3      |
| J03258 | J03258 | 601769 | GEN-2J | Vitamin D (1,25-dihydroxyvitamin D3) receptor               | 1833  | 1718C>G  | 3      |

|        |        |        |        |                                                                                                                                                          |      |          |       |
|--------|--------|--------|--------|----------------------------------------------------------------------------------------------------------------------------------------------------------|------|----------|-------|
| J03258 | J03258 | 601769 | GEN-2J | Vitamin D (1,25-dihydroxyvitamin D3) receptor                                                                                                            | 1858 | 1743G>T  | 3     |
| J03258 | J03258 | 601769 | GEN-2J | Vitamin D (1,25-dihydroxyvitamin D3) receptor                                                                                                            | 1959 | 1844A>C  | 3     |
| J03258 | J03258 | 601769 | GEN-2J | Vitamin D (1,25-dihydroxyvitamin D3) receptor                                                                                                            | 2190 | 2075delT | F     |
| J03258 | J03258 | 601769 | GEN-2J | Vitamin D (1,25-dihydroxyvitamin D3) receptor                                                                                                            | 3301 | 3186C>A  | 3     |
| J03258 | J03258 | 601769 | GEN-2J | Vitamin D (1,25-dihydroxyvitamin D3) receptor                                                                                                            | 3991 | 3876A>G  | 3     |
| J03258 | J03258 | 601769 | GEN-2J | Vitamin D (1,25-dihydroxyvitamin D3) receptor                                                                                                            | 4187 | 4072G>A  | 3     |
| J03258 | J03258 | 601769 | GEN-2J | Vitamin D (1,25-dihydroxyvitamin D3) receptor                                                                                                            | 4187 | 4072G>A  | 3     |
| J03490 | J03490 | 246900 | GEN-C5 | Dihydrolipoamide dehydrogenase (E3 component of pyruvate dehydrogenase complex, 2-oxo-glutarate complex, branched chain keto acid dehydrogenase complex) | 1569 | 1493A>C  | N498T |
| J03490 | J03490 | 246900 | GEN-C5 | Dihydrolipoamide dehydrogenase (E3 component of pyruvate dehydrogenase complex, 2-oxo-glutarate complex, branched chain keto acid dehydrogenase complex) | 1624 | 1548T>A  | 3     |
| J03490 | J03490 | 246900 | GEN-C5 | Dihydrolipoamide dehydrogenase (E3 component of pyruvate dehydrogenase complex, 2-oxo-glutarate complex, branched chain keto acid dehydrogenase complex) | 1813 | 1737A>G  | 3     |

|        |        |        |         |                                                                                                                                                                                                             |      |                 |                     |
|--------|--------|--------|---------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------|-----------------|---------------------|
| J03490 | J03490 | 246900 | GEN-C5  | branched chain keto acid dehydrogenase complex)<br>Dihydrolipoamide dehydrogenase (E3 component of pyruvate dehydrogenase complex, 2-oxo-glutarate complex, branched chain keto acid dehydrogenase complex) | 2096 | 2020T>C         | 3                   |
| J03548 | J03548 | 103260 | GEN-11M | Human adrenodoxin mRNA, complete cds                                                                                                                                                                        | 1099 | 967G>A          | 3                   |
| J03548 | J03548 | 103260 | GEN-11M | Human adrenodoxin mRNA, complete cds                                                                                                                                                                        | 1123 | 991T>C          | 3                   |
| J03548 | J03548 | 103260 | GEN-11M | Human adrenodoxin mRNA, complete cds                                                                                                                                                                        | 1222 | 1090G>C         | 3                   |
| J03548 | J03548 | 103260 | GEN-11M | Human adrenodoxin mRNA, complete cds                                                                                                                                                                        | 1254 | 1122G>A         | 3                   |
| J04144 | J04144 | 106180 | GEN-2L  | Angiotensin-converting enzyme (ACE)                                                                                                                                                                         | 501  | 479A>G          | N160S               |
| J04144 | J04144 | 106180 | GEN-2L  | Angiotensin-converting enzyme (ACE)                                                                                                                                                                         | 604  | 582C>T          | S                   |
| J04144 | J04144 | 106180 | GEN-2L  | Angiotensin-converting enzyme (ACE)                                                                                                                                                                         | 803  | 781G>T          | A261S               |
| J04144 | J04144 | 106180 | GEN-2L  | Angiotensin-converting enzyme (ACE)                                                                                                                                                                         | 1042 | 1020C>T         | S                   |
| J04144 | J04144 | 106180 | GEN-2L  | Angiotensin-converting enzyme (ACE)                                                                                                                                                                         | 1535 | 1513-1515CCT>CC | S                   |
| J04144 | J04144 | 106180 | GEN-2L  | Angiotensin-converting enzyme (ACE)                                                                                                                                                                         | 1535 | 1513-1515delCCT | [P505V;50 6-505del] |
| J04144 | J04144 | 106180 | GEN-2L  | Angiotensin-converting enzyme (ACE)                                                                                                                                                                         | 1797 | 1775A>G         | D592G               |
| J04144 | J04144 | 106180 | GEN-2L  | Angiotensin-converting enzyme (ACE)                                                                                                                                                                         | 2215 | 2193G>A         | S                   |
| J04144 | J04144 | 106180 | GEN-2L  | Angiotensin-converting enzyme (ACE)                                                                                                                                                                         | 2350 | 2328A>G         | S                   |
| J04144 | J04144 | 106180 | GEN-2L  | Angiotensin-converting enzyme (ACE)                                                                                                                                                                         | 2505 | 2483T>C         | M828T               |
| J04144 | J04144 | 106180 | GEN-2L  | Angiotensin-converting enzyme (ACE)                                                                                                                                                                         | 3409 | 3387T>C         | S                   |
| J04144 | J04144 | 106180 | GEN-2L  | Angiotensin-converting enzyme (ACE)                                                                                                                                                                         | 3409 | 3387T>C         | S                   |

|        |        |        |         |                                                                    |      |         |      |
|--------|--------|--------|---------|--------------------------------------------------------------------|------|---------|------|
| J05070 | J05070 | 120361 | GEN-16U | enzyme (ACE)<br>Human type IV<br>collagenase mRNA,<br>complete cds | 1840 | 1821A>C | S    |
| J05070 | J05070 | 120361 | GEN-16U | Human type IV<br>collagenase mRNA,<br>complete cds                 | 2101 | 2082G>A | S    |
| J05070 | J05070 | 120361 | GEN-16U | Human type IV<br>collagenase mRNA,<br>complete cds                 | 2146 | 2127C>T | 3    |
| J05070 | J05070 | 120361 | GEN-16U | Human type IV<br>collagenase mRNA,<br>complete cds                 | 2288 | 2269T>C | 3    |
| J05158 | J05158 | 603104 | GEN-173 | Human type IV<br>collagenase mRNA,<br>complete cds                 | 2314 | 2314C>T | 3    |
| J05158 | J05158 | 603104 | GEN-173 | Human carboxypeptidase<br>N mRNA, 3 end                            | 2316 | 2316G>T | 3    |
| J05158 | J05158 | 603104 | GEN-173 | Human carboxypeptidase<br>N mRNA, 3 end                            | 2332 | 2332G>T | 3    |
| J05158 | J05158 | 603104 | GEN-173 | Human carboxypeptidase<br>N mRNA, 3 end                            | 2541 | 2541G>A | 3    |
| J05158 | J05158 | 603104 | GEN-173 | Human carboxypeptidase<br>N mRNA, 3 end                            | 2651 | 2651C>T | 3    |
| K00396 | K00396 | 107741 | GEN-P0  | Human apolipoprotein E<br>(epsilon 2 and 3 alleles)<br>mRNA        | 112  | 52G>A   | A18T |
| K00396 | K00396 | 107741 | GEN-P0  | Human apolipoprotein E<br>(epsilon 2 and 3 alleles)<br>mRNA        | 121  | 61G>A   | E21K |
| K00396 | K00396 | 107741 | GEN-P0  | Human apolipoprotein E<br>(epsilon 2 and 3 alleles)<br>mRNA        | 151  | 91G>A   | E31K |
| K00396 | K00396 | 107741 | GEN-P0  | Human apolipoprotein E<br>(epsilon 2 and 3 alleles)<br>mRNA        | 197  | 137T>C  | L46P |
| K00396 | K00396 | 107741 | GEN-P0  | Human apolipoprotein E<br>(epsilon 2 and 3 alleles)<br>mRNA        | 204  | 144delG | F    |
| K00396 | K00396 | 107741 | GEN-P0  | Human apolipoprotein E<br>(epsilon 2 and 3 alleles)<br>mRNA        | 238  | 178A>G  | T60A |

|        |        |        |        |                                                             |     |        |       |
|--------|--------|--------|--------|-------------------------------------------------------------|-----|--------|-------|
| K00396 | K00396 | 107741 | GEN-P0 | Human apolipoprotein E<br>(epsilon 2 and 3 alleles)<br>mRNA | 365 | 305C>G | P102R |
| K00396 | K00396 | 107741 | GEN-P0 | Human apolipoprotein E<br>(epsilon 2 and 3 alleles)<br>mRNA | 409 | 349G>A | A117T |
| K00396 | K00396 | 107741 | GEN-P0 | Human apolipoprotein E<br>(epsilon 2 and 3 alleles)<br>mRNA | 448 | 388T>C | C130R |
| K00396 | K00396 | 107741 | GEN-P0 | Human apolipoprotein E<br>(epsilon 2 and 3 alleles)<br>mRNA | 494 | 434G>A | G145D |
| K00396 | K00396 | 107741 | GEN-P0 | Human apolipoprotein E<br>(epsilon 2 and 3 alleles)<br>mRNA | 515 | 455G>A | R152Q |
| K00396 | K00396 | 107741 | GEN-P0 | Human apolipoprotein E<br>(epsilon 2 and 3 alleles)<br>mRNA | 520 | 460C>A | R154S |
| K00396 | K00396 | 107741 | GEN-P0 | Human apolipoprotein E<br>(epsilon 2 and 3 alleles)<br>mRNA | 538 | 478C>T | R160C |
| K00396 | K00396 | 107741 | GEN-P0 | Human apolipoprotein E<br>(epsilon 2 and 3 alleles)<br>mRNA | 547 | 487C>T | R163C |
| K00396 | K00396 | 107741 | GEN-P0 | Human apolipoprotein E<br>(epsilon 2 and 3 alleles)<br>mRNA | 548 | 488G>A | R163H |
| K00396 | K00396 | 107741 | GEN-P0 | Human apolipoprotein E<br>(epsilon 2 and 3 alleles)<br>mRNA | 550 | 490A>G | K164E |
| K00396 | K00396 | 107741 | GEN-P0 | Human apolipoprotein E<br>(epsilon 2 and 3 alleles)<br>mRNA | 586 | 526C>T | R176C |
| K00396 | K00396 | 107741 | GEN-P0 | Human apolipoprotein E<br>(epsilon 2 and 3 alleles)<br>mRNA | 586 | 526C>T | R176C |
| K00396 | K00396 | 107741 | GEN-P0 | Human apolipoprotein E<br>(epsilon 2 and 3 alleles)<br>mRNA | 743 | 683G>A | F     |
| K00396 | K00396 | 107741 | GEN-P0 | Human apolipoprotein E<br>(epsilon 2 and 3 alleles)<br>mRNA | 785 | 725G>A | R242Q |

|        |        |        |         |                                                                 |      |          |       |
|--------|--------|--------|---------|-----------------------------------------------------------------|------|----------|-------|
| K00396 | K00396 | 107741 | GEN-P0  | Human apolipoprotein E<br>(epsilon 2 and 3 alleles)<br>mRNA     | 796  | 736C>T   | R246C |
| K00396 | K00396 | 107741 | GEN-P0  | Human apolipoprotein E<br>(epsilon 2 and 3 alleles)<br>mRNA     | 821  | 761T>A   | V254E |
| K00396 | K00396 | 107741 | GEN-P0  | Human apolipoprotein E<br>(epsilon 2 and 3 alleles)<br>mRNA     | 865  | 805C>G   | R269G |
| K00396 | K00396 | 107741 | GEN-P0  | Human apolipoprotein E<br>(epsilon 2 and 3 alleles)<br>mRNA     | 935  | 875G>A   | R292H |
| K00396 | K00396 | 107741 | GEN-P0  | Human apolipoprotein E<br>(epsilon 2 and 3 alleles)<br>mRNA     | 1000 | 940A>C   | S314R |
| K01911 | K01911 | 162640 | GEN-2O  | Neuropeptide Y<br>mRNA                                          | 236  | 150G>A   | S     |
| K01911 | K01911 | 162640 | GEN-2O  | Neuropeptide Y<br>mRNA                                          | 290  | 204C>T   | S     |
| K02770 | K02770 | 147720 | GEN-5M  | Interleukin 1, beta<br>mRNA                                     | 19   | (-68)A>C | 5     |
| K02770 | K02770 | 147720 | GEN-5M  | Interleukin 1, beta<br>mRNA                                     | 26   | (-61)A>C | 5     |
| K02770 | K02770 | 147720 | GEN-5M  | Interleukin 1, beta<br>mRNA                                     | 48   | (-39)C>T | 5     |
| K02770 | K02770 | 147720 | GEN-5M  | Interleukin 1, beta<br>mRNA                                     | 114  | 28G>A    | E10K  |
| K02770 | K02770 | 147720 | GEN-5M  | Interleukin 1, beta<br>mRNA                                     | 119  | 33G>A    | M11I  |
| K03195 | K03195 | 138140 | GEN-ZT  | Human (HepG2) glucose<br>transporter gene mRNA,<br>complete cds | 1484 | 1305C>T  | S     |
| K03195 | K03195 | 138140 | GEN-ZT  | Human (HepG2) glucose<br>transporter gene mRNA,<br>complete cds | 2120 | 1941G>C  | 3     |
| KDR    | X61656 | 191306 | GEN-3BZ | H.sapiens mRNA for<br>growth factor receptor<br>tyrosine kinase | 2308 | 2308A>G  | T770A |
| KDR    | X61656 | 191306 | GEN-3BZ | H.sapiens mRNA for<br>growth factor receptor<br>tyrosine kinase | 2353 | 2353G>C  | G785R |
| KDR    | X61656 | 191306 | GEN-3BZ | H.sapiens mRNA for<br>growth factor receptor<br>tyrosine kinase | 2499 | 2499C>G  | N833K |
| KDR    | X61656 | 191306 | GEN-3BZ | H.sapiens mRNA for<br>growth factor receptor<br>tyrosine kinase | 2537 | 2537A>T  | E846V |

|        |        |        |         |                                                                               |      |         |   |
|--------|--------|--------|---------|-------------------------------------------------------------------------------|------|---------|---|
| KDR    | X61656 | 191306 | GEN-3BZ | tyrosine kinase<br>H.sapiens mRNA for<br>growth factor receptor               | 4123 | 4123G>C | 3 |
| L00352 | L00352 | 143890 | GEN-2S8 | tyrosine kinase<br>Human low density<br>lipoprotein receptor gene,<br>exon 18 | 71   | 72C>T   | 3 |
| L00352 | L00352 | 143890 | GEN-2S8 | Human low density<br>lipoprotein receptor gene,<br>exon 18                    | 103  | 104G>A  | 3 |
| L00352 | L00352 | 143890 | GEN-2S8 | Human low density<br>lipoprotein receptor gene,<br>exon 18                    | 716  | 717C>T  | 3 |
| L00352 | L00352 | 143890 | GEN-2S8 | Human low density<br>lipoprotein receptor gene,<br>exon 18                    | 881  | 882G>A  | 3 |
| L00352 | L00352 | 143890 | GEN-2S8 | Human low density<br>lipoprotein receptor gene,<br>exon 18                    | 1180 | 1181A>G | 3 |
| L00352 | L00352 | 143890 | GEN-2S8 | Human low density<br>lipoprotein receptor gene,<br>exon 18                    | 1186 | 1187C>G | 3 |
| L00352 | L00352 | 143890 | GEN-2S8 | Human low density<br>lipoprotein receptor gene,<br>exon 18                    | 1187 | 1188T>G | 3 |
| L00352 | L00352 | 143890 | GEN-2S8 | Human low density<br>lipoprotein receptor gene,<br>exon 18                    | 1191 | 1192G>A | 3 |
| L00352 | L00352 | 143890 | GEN-2S8 | Human low density<br>lipoprotein receptor gene,<br>exon 18                    | 1222 | 1223G>A | 3 |
| L00352 | L00352 | 143890 | GEN-2S8 | Human low density<br>lipoprotein receptor gene,<br>exon 18                    | 1223 | 1224C>T | 3 |
| L00352 | L00352 | 143890 | GEN-2S8 | Human low density<br>lipoprotein receptor gene,<br>exon 18                    | 1224 | 1225G>A | 3 |
| L00352 | L00352 | 143890 | GEN-2S8 | Human low density<br>lipoprotein receptor gene,<br>exon 18                    | 1227 | 1228T>C | 3 |
| L00352 | L00352 | 143890 | GEN-2S8 | Human low density<br>lipoprotein receptor gene,<br>exon 18                    | 1234 | 1235T>C | 3 |

|        |         |        |     |                                                      |      |         |   |
|--------|---------|--------|-----|------------------------------------------------------|------|---------|---|
| L00352 | L00352  | 143890 | 2S8 | lipoprotein receptor gene, exon 18                   | 1252 | 1253A>T | 3 |
| L00352 | GEN-2S8 |        |     | Human low density lipoprotein receptor gene, exon 18 |      |         |   |
| L00352 | L00352  | 143890 | 2S8 | lipoprotein receptor gene, exon 18                   | 1268 | 1269A>C | 3 |
| L00352 | GEN-2S8 |        |     | Human low density lipoprotein receptor gene, exon 18 |      |         |   |
| L00352 | L00352  | 143890 | 2S8 | lipoprotein receptor gene, exon 18                   | 1268 | 1269A>T | 3 |
| L00352 | GEN-2S8 |        |     | Human low density lipoprotein receptor gene, exon 18 |      |         |   |
| L00352 | L00352  | 143890 | 2S8 | lipoprotein receptor gene, exon 18                   | 1279 | 1280C>T | 3 |
| L00352 | GEN-2S8 |        |     | Human low density lipoprotein receptor gene, exon 18 |      |         |   |
| L00352 | L00352  | 143890 | 2S8 | lipoprotein receptor gene, exon 18                   | 1280 | 1281G>A | 3 |
| L00352 | GEN-2S8 |        |     | Human low density lipoprotein receptor gene, exon 18 |      |         |   |
| L00352 | L00352  | 143890 | 2S8 | lipoprotein receptor gene, exon 18                   | 1308 | 1309C>T | 3 |
| L00352 | GEN-2S8 |        |     | Human low density lipoprotein receptor gene, exon 18 |      |         |   |
| L00352 | L00352  | 143890 | 2S8 | lipoprotein receptor gene, exon 18                   | 1309 | 1310G>A | 3 |
| L00352 | GEN-2S8 |        |     | Human low density lipoprotein receptor gene, exon 18 |      |         |   |
| L00352 | L00352  | 143890 | 2S8 | lipoprotein receptor gene, exon 18                   | 1316 | 1317G>A | 3 |
| L00352 | GEN-2S8 |        |     | Human low density lipoprotein receptor gene, exon 18 |      |         |   |
| L00352 | L00352  | 143890 | 2S8 | lipoprotein receptor gene, exon 18                   | 1320 | 1321T>C | 3 |
| L00352 | GEN-2S8 |        |     | Human low density lipoprotein receptor gene, exon 18 |      |         |   |
| L00352 | L00352  | 143890 | 2S8 | lipoprotein receptor gene, exon 18                   | 1345 | 1346G>A | 3 |
| L00352 | GEN-2S8 |        |     | Human low density lipoprotein receptor gene, exon 18 |      |         |   |
| L00352 | L00352  | 143890 | 2S8 | lipoprotein receptor gene, exon 18                   | 1368 | 1369T>C | 3 |
| L00352 | GEN-2S8 |        |     | Human low density lipoprotein receptor gene, exon 18 |      |         |   |
| L00352 | L00352  | 143890 | 2S8 | lipoprotein receptor gene, exon 18                   | 1376 | 1377C>T | 3 |
| L00352 | GEN-2S8 |        |     | Human low density lipoprotein receptor gene, exon 18 |      |         |   |
| L00352 | L00352  | 143890 | 2S8 | lipoprotein receptor gene, exon 18                   | 1383 | 1384C>T | 3 |
| L00352 | GEN-2S8 |        |     | Human low density lipoprotein receptor gene, exon 18 |      |         |   |



|        |        |        |         |                                                                                |      |         |   |
|--------|--------|--------|---------|--------------------------------------------------------------------------------|------|---------|---|
| L00352 | L00352 | 143890 | GEN-2S8 | Human low density lipoprotein receptor gene, exon 18                           | 1406 | 1407T>C | 3 |
| L00352 | L00352 | 143890 | GEN-2S8 | Human low density lipoprotein receptor gene, exon 18                           | 1418 | 1419G>C | 3 |
| L00352 | L00352 | 143890 | GEN-2S8 | Human low density lipoprotein receptor gene, exon 18                           | 1428 | 1429T>C | 3 |
| L00352 | L00352 | 143890 | GEN-2S8 | Human low density lipoprotein receptor gene, exon 18                           | 1453 | 1454C>T | 3 |
| L00352 | L00352 | 143890 | GEN-2S8 | Human low density lipoprotein receptor gene, exon 18                           | 1796 | 1797T>C | 3 |
| L00352 | L00352 | 143890 | GEN-2S8 | Human low density lipoprotein receptor gene, exon 18                           | 2108 | 2109G>A | 3 |
| L00352 | L00352 | 143890 | GEN-2S8 | Human low density lipoprotein receptor gene, exon 18                           | 2490 | 2491A>C | 3 |
| L02932 | L02932 | 170998 | GEN-KW4 | Human peroxisome proliferator activated receptor mRNA, complete cds            | 648  | 432G>A  | S |
| L07592 | L07592 | 600409 | GEN-1E7 | Human peroxisome proliferator activated receptor mRNA, complete cds            | 3119 | 2782C>G | 3 |
| L13286 | L13286 | 600125 | GEN-1O3 | Human mitochondrial 1,25-dihydroxyvitamin D3 24-hydroxylase mRNA, complete cds | 2031 | 1638G>A | 3 |
| L13436 | L13436 | 108961 | GEN-2Q  | guanylate cyclase                                                              | 1410 | 1411T>A | 3 |
| L13436 | L13436 | 108961 | GEN-2Q  | guanylate cyclase                                                              | 1646 | 1647C>G | 3 |
| L13436 | L13436 | 108961 | GEN-2Q  | guanylate cyclase                                                              | 1650 | 1651G>C | 3 |
| L13436 | L13436 | 108961 | GEN-2Q  | guanylate cyclase                                                              | 1677 | 1678C>G | 3 |
| L13436 | L13436 | 108961 | GEN-2Q  | guanylate cyclase                                                              | 2222 | 2223C>T | 3 |
| L13436 | L13436 | 108961 | GEN-2Q  | guanylate cyclase                                                              | 2444 | 2445C>T | 3 |
| L13858 | L13858 | 182530 | GEN-    | Human guanine nucleotide                                                       | 423  | 423T>C  | S |

|        |        |        |         |                                                                                                             |      |          |       |
|--------|--------|--------|---------|-------------------------------------------------------------------------------------------------------------|------|----------|-------|
| L13858 | L13858 | 182530 | GEN-1PL | exchange factor mRNA, complete cds                                                                          | 3957 | 3957G>A  | S     |
| L17075 | L17075 | 601284 | GEN-1ZQ | Human guanine nucleotide exchange factor mRNA, complete cds                                                 | 838  | 747G>A   | S     |
| L19182 | L19182 | 602867 | GEN-21Z | Human TGF- $\beta$ superfamily receptor type I mRNA, complete cds                                           | 297  | 284G>A   | R95K  |
| L20859 | L20859 | 137570 | GEN-23V | Human MAC25 mRNA, complete cds                                                                              | 3141 | 2771A>G  | 3     |
| L26232 | L26232 | 172425 | GEN-2AK | Human leukemia virus receptor 1 (GLVR1) mRNA, complete cds                                                  | 906  | 819C>T   | S     |
| L26232 | L26232 | 172425 | GEN-2AK | Human phospholipid transfer protein mRNA, complete cds                                                      | 1547 | 1460C>A  | T487K |
| L27080 | L27080 | None   | GEN-4G2 | Human phospholipid transfer protein mRNA, complete cds                                                      | 146  | (-38)A>C | 5     |
| L27080 | L27080 | None   | GEN-4G2 | Human melanocortin 5 receptor (MC5R) gene, complete cds                                                     | 927  | 744C>T   | S     |
| L40992 | L40992 | 600211 | GEN-2SO | Human melanocortin 5 receptor (MC5R) gene, complete cds                                                     | 265  | 265G>A   | V89I  |
| L78207 | L78207 | 600509 | GEN-5Q  | Homo sapiens (clone PEBP2aA1) core-binding factor, runt domain, alpha subunit 1 (CBFA1) mRNA, 3' end of cds | 4019 | 3981A>G  | S     |
| LEPR   | U43168 | 601007 | GEN-2UN | Cell surface receptor for sulfonyleureas on pancreatic b cells                                              | 446  | 253A>G   | T85A  |
| LEPR   | U43168 | 601007 | GEN-2UN | Human leptin receptor (Ob-r) mRNA, complete cds                                                             | 519  | 326A>G   | K109R |
| LEPR   | U43168 | 601007 | GEN-2UN | Human leptin receptor (Ob-r) mRNA, complete cds                                                             | 861  | 668A>G   | Q223R |
| LEPR   | U43168 | 601007 | GEN-2UN | Human leptin receptor (Ob-r) mRNA, complete cds                                                             | 1222 | 1029T>C  | S     |

|        |        |        |         |                                                                            |      |         |       |
|--------|--------|--------|---------|----------------------------------------------------------------------------|------|---------|-------|
| LEPR   | U43168 | 601007 | GEN-2UN | Human leptin receptor (Ob-r) mRNA, complete cds                            | 2161 | 1968G>C | K656N |
| LEPR   | U43168 | 601007 | GEN-2UN | Human leptin receptor (Ob-r) mRNA, complete cds                            | 2174 | 1981A>C | T661P |
| LEPR   | U43168 | 601007 | GEN-2UN | Human leptin receptor (Ob-r) mRNA, complete cds                            | 2764 | 2571T>G | S     |
| LEPR   | U43168 | 601007 | GEN-2UN | Human leptin receptor (Ob-r) mRNA, complete cds                            | 3151 | 2958C>T | S     |
| LEPR   | U43168 | 601007 | GEN-2UN | Human leptin receptor (Ob-r) mRNA, complete cds                            | 3250 | 3057G>A | S     |
| LIPA   | X76488 | 278000 | GEN-3P2 | H.sapiens mRNA for lysosomal acid lipase                                   | 191  | 46A>C   | T16P  |
| LIPA   | X76488 | 278000 | GEN-3P2 | H.sapiens mRNA for lysosomal acid lipase                                   | 212  | 67G>A   | G23R  |
| LIPA   | X76488 | 278000 | GEN-3P2 | H.sapiens mRNA for lysosomal acid lipase                                   | 967  | 822G>A  | M274I |
| LIPA   | X76488 | 278000 | GEN-3P2 | H.sapiens mRNA for lysosomal acid lipase                                   | 1531 | 1386C>T | 3     |
| LIPA   | X76488 | 278000 | GEN-3P2 | H.sapiens mRNA for lysosomal acid lipase                                   | 2254 | 2109A>T | 3     |
| LIPA   | X76488 | 278000 | GEN-3P2 | H.sapiens mRNA for lysosomal acid lipase                                   | 2439 | 2294C>T | 3     |
| LIPC   | J03540 | 151670 | GEN-11J | Human hepatic lipase mRNA, complete cds                                    | 469  | 465T>G  | S     |
| LIPC   | J03540 | 151670 | GEN-11J | Human hepatic lipase mRNA, complete cds                                    | 595  | 591A>G  | S     |
| LIPC   | J03540 | 151670 | GEN-11J | Human hepatic lipase mRNA, complete cds                                    | 648  | 644G>A  | S215N |
| LIPC   | J03540 | 151670 | GEN-11J | Human hepatic lipase mRNA, complete cds                                    | 817  | 813C>T  | S     |
| LIPC   | J03540 | 151670 | GEN-11J | Human hepatic lipase mRNA, complete cds                                    | 1441 | 1437C>A | S     |
| LRP1   | D90070 | 107770 | GEN-466 | Human ATL-derived PMA-responsive (APR) peptide mRNA                        | 686  | 513T>G  | 3     |
| LRPAP1 | M63959 | 104225 | GEN-3EI | Human alpha-2-macroglobulin receptor-associated protein mRNA, complete cds | 850  | 837G>A  | S     |
| LRPAP1 | M63959 | 104225 | GEN-3EI | Human alpha-2-macroglobulin receptor-associated protein mRNA, complete cds | 1093 | 1080C>T | 3     |

|        |        |        |             |                                                                                       |      |                    |       |
|--------|--------|--------|-------------|---------------------------------------------------------------------------------------|------|--------------------|-------|
| LRPAP1 | M63959 | 104225 | GEN-3EI     | associated protein mRNA,<br>complete cds                                              | 1175 | 1162G>A            | 3     |
|        |        |        |             | Human alpha-2-<br>macroglobulin receptor-<br>associated protein mRNA,<br>complete cds |      |                    |       |
| LRPAP1 | M63959 | 104225 | GEN-3EI     | Human alpha-2-<br>macroglobulin receptor-<br>associated protein mRNA,<br>complete cds | 1249 | 1236C>T            | 3     |
|        |        |        |             | Human alpha-2-<br>macroglobulin receptor-<br>associated protein mRNA,<br>complete cds |      |                    |       |
| LRPAP1 | M63959 | 104225 | GEN-3EI     | Human alpha-2-<br>macroglobulin receptor-<br>associated protein mRNA,<br>complete cds | 1249 | 1236C>T            | 3     |
|        |        |        |             | Human alpha-2-<br>macroglobulin receptor-<br>associated protein mRNA,<br>complete cds |      |                    |       |
| LRPAP1 | M63959 | 104225 | GEN-3EI     | Human alpha-2-<br>macroglobulin receptor-<br>associated protein mRNA,<br>complete cds | 1392 | 1379T>G            | 3     |
|        |        |        |             | Human alpha-2-<br>macroglobulin receptor-<br>associated protein mRNA,<br>complete cds |      |                    |       |
| M10051 | M10051 | 147670 | GEN-2V      | Insulin receptor                                                                      | 2757 | 2619G>A            | S     |
| M10051 | M10051 | 147670 | GEN-2V      | Insulin receptor                                                                      | 4391 | 4253G>A            | 3     |
| M10901 | M10901 | 138040 | GEN-2W      | Corticosteroid nuclear<br>receptor b                                                  | 1220 | 1088A>G            | N363S |
| M10901 | M10901 | 138040 | GEN-2W      | Corticosteroid nuclear<br>receptor b                                                  | 2024 | 1892-<br>1893AG>AG | S     |
| M10901 | M10901 | 138040 | GEN-2W      | Corticosteroid nuclear<br>receptor b                                                  | 2024 | 1892-<br>1893delAG | F     |
| M10901 | M10901 | 138040 | GEN-2W      | Corticosteroid nuclear<br>receptor b                                                  | 2054 | 1922A>T            | D641V |
| M10901 | M10901 | 138040 | GEN-2W      | Corticosteroid nuclear<br>receptor b                                                  | 2372 | 2240T>G            | I747S |
| M10901 | M10901 | 138040 | GEN-2W      | Corticosteroid nuclear<br>receptor b                                                  | 2391 | 2259A>C            | L753F |
| M10901 | M10901 | 138040 | GEN-2W      | Corticosteroid nuclear<br>receptor b                                                  | 2391 | 2259A>T            | L753F |
| M11050 | M11050 | 138040 | GEN-7Y      | Glucocorticoid receptor                                                               | 2166 | 2034C>T            | S     |
| M11050 | M11050 | 138040 | GEN-7Y      | Glucocorticoid receptor                                                               | 3353 | 3221T>G            | 3     |
| M11050 | M11050 | 138040 | GEN-7Y      | Glucocorticoid receptor                                                               | 3398 | 3266T>G            | 3     |
| M11717 | M11717 | 140550 | GEN-<br>MF3 | Human heat shock protein<br>(hsp 70) gene, complete<br>cds                            | 54   | (-162)G>A          | 5     |

|        |        |        |         |                                                                |      |          |       |
|--------|--------|--------|---------|----------------------------------------------------------------|------|----------|-------|
| M11717 | M11717 | 140550 | GEN-MF3 | Human heat shock protein (hsp 70) gene, complete cds           | 190  | (-26)C>G | 5     |
| M11717 | M11717 | 140550 | GEN-MF3 | Human heat shock protein (hsp 70) gene, complete cds           | 320  | 105C>T   | S     |
| M11717 | M11717 | 140550 | GEN-MF3 | Human heat shock protein (hsp 70) gene, complete cds           | 390  | 175G>A   | V59M  |
| M11717 | M11717 | 140550 | GEN-MF3 | Human heat shock protein (hsp 70) gene, complete cds           | 431  | 216C>G   | S     |
| M11717 | M11717 | 140550 | GEN-MF3 | Human heat shock protein (hsp 70) gene, complete cds           | 545  | 330G>C   | E110D |
| M11717 | M11717 | 140550 | GEN-MF3 | Human heat shock protein (hsp 70) gene, complete cds           | 1907 | 1692C>G  | S     |
| M11717 | M11717 | 140550 | GEN-MF3 | Human heat shock protein (hsp 70) gene, complete cds           | 2319 | 2104A>G  | 3     |
| M12578 | M12578 | 152760 | GEN-2Y  | Gonadotropin-releasing hormone (leutinizing-releasing hormone) | 79   | 47G>C    | W16S  |
| M12674 | M12674 | 133430 | GEN-7Z  | Estrogen receptor                                              | 1267 | 975C>G   | S     |
| M13509 | M13509 | 120353 | GEN-QJ  | Human skin collagenase mRNA, complete cds                      | 383  | 315A>G   | S     |
| M13509 | M13509 | 120353 | GEN-QJ  | Human skin collagenase mRNA, complete cds                      | 899  | 831G>A   | S     |
| M13509 | M13509 | 120353 | GEN-QJ  | Human skin collagenase mRNA, complete cds                      | 1522 | 1454A>G  | 3     |
| M13509 | M13509 | 120353 | GEN-QJ  | Human skin collagenase mRNA, complete cds                      | 1747 | 1679C>T  | 3     |
| M14221 | M14221 | 161565 | GEN-QM  | Human cathepsin B proteinase mRNA, complete cds                | 184  | (-11)T>C | 5     |
| M14221 | M14221 | 161565 | GEN-QM  | Human cathepsin B proteinase mRNA, complete cds                | 270  | 76G>C    | V26L  |
| M14221 | M14221 | 161565 | GEN-QM  | Human cathepsin B proteinase mRNA, complete cds                | 446  | 252C>T   | S     |

|        |        |        |        |                                                       |      |         |       |
|--------|--------|--------|--------|-------------------------------------------------------|------|---------|-------|
| M14221 | M14221 | 161565 | GEN-QM | Human cathepsin B<br>proteinase mRNA,<br>complete cds | 1254 | 1060C>G | 3     |
| M14221 | M14221 | 161565 | GEN-QM | Human cathepsin B<br>proteinase mRNA,<br>complete cds | 1306 | 1112G>A | 3     |
| M14221 | M14221 | 161565 | GEN-QM | Human cathepsin B<br>proteinase mRNA,<br>complete cds | 1336 | 1142T>A | 3     |
| M14221 | M14221 | 161565 | GEN-QM | Human cathepsin B<br>proteinase mRNA,<br>complete cds | 1338 | 1144C>T | 3     |
| M14221 | M14221 | 161565 | GEN-QM | Human cathepsin B<br>proteinase mRNA,<br>complete cds | 1451 | 1257G>A | 3     |
| M14221 | M14221 | 161565 | GEN-QM | Human cathepsin B<br>proteinase mRNA,<br>complete cds | 1462 | 1268C>T | 3     |
| M14221 | M14221 | 161565 | GEN-QM | Human cathepsin B<br>proteinase mRNA,<br>complete cds | 1522 | 1328G>C | 3     |
| M14221 | M14221 | 161565 | GEN-QM | Human cathepsin B<br>proteinase mRNA,<br>complete cds | 1557 | 1363G>C | 3     |
| M14221 | M14221 | 161565 | GEN-QM | Human cathepsin B<br>proteinase mRNA,<br>complete cds | 1585 | 1391C>A | 3     |
| M14221 | M14221 | 161565 | GEN-QM | Human cathepsin B<br>proteinase mRNA,<br>complete cds | 1630 | 1436T>C | 3     |
| M14221 | M14221 | 161565 | GEN-QM | Human cathepsin B<br>proteinase mRNA,<br>complete cds | 1668 | 1474T>G | 3     |
| M14221 | M14221 | 161565 | GEN-QM | Human cathepsin B<br>proteinase mRNA,<br>complete cds | 1712 | 1518C>G | 3     |
| M14221 | M14221 | 161565 | GEN-QM | Human cathepsin B<br>proteinase mRNA,<br>complete cds | 1898 | 1704A>G | 3     |
| M14565 | M14565 | 118485 | GEN-30 | Cytochrome P450,<br>complete cds                      | 947  | 903G>C  | M301I |

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|        |        |        |         |                                                          |      |          |       |
|--------|--------|--------|---------|----------------------------------------------------------|------|----------|-------|
| M15856 | M15856 | 238600 | GEN-33  | Lipoprotein lipase                                       | 836  | 662T>C   | I221T |
| M15856 | M15856 | 238600 | GEN-33  | Lipoprotein lipase                                       | 839  | 665G>A   | G222E |
| M15856 | M15856 | 238600 | GEN-33  | Lipoprotein lipase                                       | 843  | 669C>T   | S     |
| M15856 | M15856 | 238600 | GEN-33  | Lipoprotein lipase                                       | 867  | 693C>G   | D231E |
| M15856 | M15856 | 238600 | GEN-33  | Lipoprotein lipase                                       | 875  | 701C>T   | P234L |
| M15856 | M15856 | 238600 | GEN-33  | Lipoprotein lipase                                       | 916  | 742delG  | F     |
| M15856 | M15856 | 238600 | GEN-33  | Lipoprotein lipase                                       | 983  | 809G>A   | R270H |
| M15856 | M15856 | 238600 | GEN-33  | Lipoprotein lipase                                       | 985  | 811T>A   | S271T |
| M15856 | M15856 | 238600 | GEN-33  | Lipoprotein lipase                                       | 1003 | 829G>A   | D277N |
| M15856 | M15856 | 238600 | GEN-33  | Lipoprotein lipase                                       | 1127 | 953A>G   | N318S |
| M15856 | M15856 | 238600 | GEN-33  | Lipoprotein lipase                                       | 1255 | 1081G>A  | A361T |
| M15856 | M15856 | 238600 | GEN-33  | Lipoprotein lipase                                       | 1348 | 1174C>G  | L392V |
| M15856 | M15856 | 238600 | GEN-33  | Lipoprotein lipase                                       | 1401 | 1227G>A  | F     |
| M15856 | M15856 | 238600 | GEN-33  | Lipoprotein lipase                                       | 1508 | 1334G>A  | C445Y |
| M15856 | M15856 | 238600 | GEN-33  | Lipoprotein lipase                                       | 1553 | 1379C>T  | A460V |
| M15856 | M15856 | 238600 | GEN-33  | Lipoprotein lipase                                       | 1595 | 1421C>G  | F     |
| M15856 | M15856 | 238600 | GEN-33  | Lipoprotein lipase                                       | 1611 | 1437G>A  | 3     |
| M15856 | M15856 | 238600 | GEN-33  | Lipoprotein lipase                                       | 1973 | 1799T>C  | 3     |
| M15856 | M15856 | 238600 | GEN-33  | Lipoprotein lipase                                       | 2428 | 2254T>A  | 3     |
| M15856 | M15856 | 238600 | GEN-33  | Lipoprotein lipase                                       | 2743 | 2569T>C  | 3     |
| M15856 | M15856 | 238600 | GEN-33  | Lipoprotein lipase                                       | 2851 | 2677A>G  | 3     |
| M15856 | M15856 | 238600 | GEN-33  | Lipoprotein lipase                                       | 2851 | 2677A>G  | 3     |
| M15856 | M15856 | 238600 | GEN-33  | Lipoprotein lipase                                       | 2958 | 2784G>A  | 3     |
| M15856 | M15856 | 238600 | GEN-33  | Lipoprotein lipase                                       | 3017 | 2843T>C  | 3     |
| M15856 | M15856 | 238600 | GEN-33  | Lipoprotein lipase                                       | 3272 | 3098T>C  | 3     |
| M15856 | M15856 | 238600 | GEN-33  | Lipoprotein lipase                                       | 3272 | 3098T>C  | 3     |
| M15856 | M15856 | 238600 | GEN-33  | Lipoprotein lipase                                       | 3343 | 3169T>C  | 3     |
| M15856 | M15856 | 238600 | GEN-33  | Lipoprotein lipase                                       | 3447 | 3273C>T  | 3     |
| M16660 | M16660 | 140571 | GEN-1YC | Human 90-kDa heat-shock protein gene, cDNA, complete cds | 825  | 741G>A   | S     |
| M16660 | M16660 | 140571 | GEN-1YC | Human 90-kDa heat-shock protein gene, cDNA, complete cds | 825  | 741G>A   | S     |
| M16801 | M16801 | 600983 | GEN-36  | Mineralocorticoid receptor (aldosterone receptor)        | 175  | (-42)C>G | 5     |
| M16801 | M16801 | 600983 | GEN-36  | Mineralocorticoid receptor                               | 754  | 538A>G   | I180V |



|        |        |        |         |                                                                  |      |          |       |
|--------|--------|--------|---------|------------------------------------------------------------------|------|----------|-------|
| M16801 | M16801 | 600983 | GEN-36  | (aldosterone receptor)                                           | 938  | 722C>T   | A241V |
|        |        |        |         | Mineralocorticoid receptor                                       |      |          |       |
| M16801 | M16801 | 600983 | GEN-36  | (aldosterone receptor)                                           | 1221 | 1005delC | F     |
|        |        |        |         | Mineralocorticoid receptor                                       |      |          |       |
| M16801 | M16801 | 600983 | GEN-36  | (aldosterone receptor)                                           | 1591 | 1375delT | F     |
|        |        |        |         | Mineralocorticoid receptor                                       |      |          |       |
| M16801 | M16801 | 600983 | GEN-36  | (aldosterone receptor)                                           | 1713 | 1497C>T  | S     |
|        |        |        |         | Mineralocorticoid receptor                                       |      |          |       |
| M16801 | M16801 | 600983 | GEN-36  | (aldosterone receptor)                                           | 1825 | 1609C>T  | F     |
|        |        |        |         | Mineralocorticoid receptor                                       |      |          |       |
| M16801 | M16801 | 600983 | GEN-36  | (aldosterone receptor)                                           | 2438 | 2222T>G  | V741G |
|        |        |        |         | Mineralocorticoid receptor                                       |      |          |       |
| M16801 | M16801 | 600983 | GEN-36  | (aldosterone receptor)                                           | 2730 | 2514G>A  | S     |
|        |        |        |         | Mineralocorticoid receptor                                       |      |          |       |
| M16801 | M16801 | 600983 | GEN-36  | (aldosterone receptor)                                           | 5243 | 5027T>A  | 3     |
|        |        |        |         | Mineralocorticoid receptor                                       |      |          |       |
| M16801 | M16801 | 600983 | GEN-36  | (aldosterone receptor)                                           | 5645 | 5429G>A  | 3     |
|        |        |        |         | Mineralocorticoid receptor                                       |      |          |       |
| M16827 | M16827 | 201450 | GEN-EI  | (aldosterone receptor)                                           | 1956 | 1938T>C  | 3     |
|        |        |        |         | Acyl-Coenzyme A                                                  |      |          |       |
|        |        |        |         | dehydrogenase, C-4 to C-12 straight chain                        |      |          |       |
| M20132 | M20132 | 313700 | GEN-38  | Androgen receptor                                                | 995  | 633G>A   | S     |
|        |        |        |         | (dihydrotestosterone receptor)                                   |      |          |       |
| M20132 | M20132 | 313700 | GEN-38  | Androgen receptor                                                | 1385 | 1023T>C  | S     |
|        |        |        |         | (dihydrotestosterone receptor)                                   |      |          |       |
| M20132 | M20132 | 313700 | GEN-38  | Androgen receptor                                                | 1786 | 1424G>A  | G475E |
|        |        |        |         | (dihydrotestosterone receptor)                                   |      |          |       |
| M20566 | M20566 | 147880 | GEN-3A  | Interleukin 6A                                                   | 3058 | 2621A>T  | 3     |
| M20681 | M20681 | 138170 | GEN-230 | Human glucose transporter-like protein-III (GLUT3), complete cds | 1550 | 1308C>T  | S     |
|        |        |        |         | Human glucose transporter-like protein-III (GLUT3), complete cds |      |          |       |
| M20681 | M20681 | 138170 | GEN-230 | Human glucose transporter-like protein-III (GLUT3), complete cds | 3179 | 2937T>C  | 3     |
|        |        |        |         | Human glucose transporter-like protein-III (GLUT3), complete cds |      |          |       |
| M20681 | M20681 | 138170 | GEN-230 | Human glucose transporter-like protein-III (GLUT3), complete cds | 3238 | 2996C>T  | 3     |
|        |        |        |         | Human glucose transporter-like protein-III (GLUT3), complete cds |      |          |       |

|        |        |        |         |                                                                  |      |         |       |
|--------|--------|--------|---------|------------------------------------------------------------------|------|---------|-------|
| M20681 | M20681 | 138170 | GEN-230 | Human glucose transporter-like protein-III (GLUT3), complete cds | 3356 | 3114T>C | 3     |
| M20681 | M20681 | 138170 | GEN-230 | Human glucose transporter-like protein-III (GLUT3), complete cds | 3378 | 3136T>C | 3     |
| M20681 | M20681 | 138170 | GEN-230 | Human glucose transporter-like protein-III (GLUT3), complete cds | 3524 | 3282C>A | 3     |
| M20681 | M20681 | 138170 | GEN-230 | Human glucose transporter-like protein-III (GLUT3), complete cds | 3572 | 3330G>T | 3     |
| M23725 | M23725 | 179050 | GEN-ES  | Pyruvate kinase, muscle                                          | 547  | 438C>T  | S     |
| M23725 | M23725 | 179050 | GEN-ES  | Pyruvate kinase, muscle                                          | 850  | 741G>A  | S     |
| M23725 | M23725 | 179050 | GEN-ES  | Pyruvate kinase, muscle                                          | 1259 | 1150G>A | E384K |
| M24857 | M24857 | 180190 | GEN-80  | Retinoic acid receptor, gamma 1                                  | 1694 | 1280C>T | S427L |
| M26393 | M26393 | 201470 | GEN-EW  | Acyl-Coenzyme A dehydrogenase, C-2 to C-3 short chain            | 1797 | 1765A>G | 3     |
| M27137 | M27137 | 109715 | GEN-5W  | 3beta hydroxysteroid dehydrogenase                               | 1103 | 1100C>A | T367N |
| M27492 | M27492 | 147810 | GEN-3F  | INTERLEUKIN 1 RECEPTOR, TYPE I                                   | 4686 | 4604T>G | 3     |
| M27875 | M27875 | 107680 | GEN-2CK | Human apolipoprotein A-I mRNA, complete cds                      | 34   | 15G>C   | S     |
| M27875 | M27875 | 107680 | GEN-2CK | Human apolipoprotein A-I mRNA, complete cds                      | 202  | 183C>T  | S     |
| M27875 | M27875 | 107680 | GEN-2CK | Human apolipoprotein A-I mRNA, complete cds                      | 204  | 185T>G  | L62W  |
| M27875 | M27875 | 107680 | GEN-2CK | Human apolipoprotein A-I mRNA, complete cds                      | 255  | 236C>T  | S79F  |
| M27875 | M27875 | 107680 | GEN-2CK | Human apolipoprotein A-I mRNA, complete cds                      | 689  | 670C>T  | S     |
| M27875 | M27875 | 107680 | GEN-2CK | Human apolipoprotein A-I mRNA, complete cds                      | 824  | 805G>A  | 3     |
| M28614 | M28614 | 107720 | GEN-6Q  | Human apolipoprotein A-I mRNA, complete cds                      | 370  | 340C>G  | 3     |
| M28614 | M28614 | 107720 | GEN-6Q  | Human apolipoprotein A-I mRNA, complete cds                      | 401  | 371T>G  | 3     |
| M28614 | M28614 | 107720 | GEN-6Q  | Human apolipoprotein A-I mRNA, complete cds                      | 479  | 449T>A  | 3     |

|        |        |        |        |                                                                                 |     |        |      |
|--------|--------|--------|--------|---------------------------------------------------------------------------------|-----|--------|------|
| M29882 | M29882 | 107670 | GEN-6R | Apolipoprotein A-II                                                             | 26  | 17C>A  | A6E  |
| M29882 | M29882 | 107670 | GEN-6R | Apolipoprotein A-II                                                             | 183 | 174G>A | S    |
| M29882 | M29882 | 107670 | GEN-6R | Apolipoprotein A-II                                                             | 192 | 183C>A | S    |
| M30262 | M30262 | 600295 | GEN-WA | Human cardiolipin-atrial<br>natriuretic factor (CDD-<br>ANF) mRNA, complete cds | 178 | 79C>T  | P27S |
| M30262 | M30262 | 600295 | GEN-WA | Human cardiolipin-atrial<br>natriuretic factor (CDD-<br>ANF) mRNA, complete cds | 178 | 79C>T  | P27S |
| M30262 | M30262 | 600295 | GEN-WA | Human cardiolipin-atrial<br>natriuretic factor (CDD-<br>ANF) mRNA, complete cds | 203 | 104C>G | A35G |
| M30262 | M30262 | 600295 | GEN-WA | Human cardiolipin-atrial<br>natriuretic factor (CDD-<br>ANF) mRNA, complete cds | 203 | 104C>G | A35G |
| M30262 | M30262 | 600295 | GEN-WA | Human cardiolipin-atrial<br>natriuretic factor (CDD-<br>ANF) mRNA, complete cds | 210 | 111G>T | S    |
| M30262 | M30262 | 600295 | GEN-WA | Human cardiolipin-atrial<br>natriuretic factor (CDD-<br>ANF) mRNA, complete cds | 210 | 111G>T | S    |
| M30262 | M30262 | 600295 | GEN-WA | Human cardiolipin-atrial<br>natriuretic factor (CDD-<br>ANF) mRNA, complete cds | 327 | 228C>T | S    |
| M30262 | M30262 | 600295 | GEN-WA | Human cardiolipin-atrial<br>natriuretic factor (CDD-<br>ANF) mRNA, complete cds | 327 | 228C>T | S    |
| M30262 | M30262 | 600295 | GEN-WA | Human cardiolipin-atrial<br>natriuretic factor (CDD-<br>ANF) mRNA, complete cds | 553 | 454T>C | F    |
| M30262 | M30262 | 600295 | GEN-WA | Human cardiolipin-atrial<br>natriuretic factor (CDD-<br>ANF) mRNA, complete cds | 553 | 454T>C | F    |
| M30262 | M30262 | 600295 | GEN-WA | Human cardiolipin-atrial<br>natriuretic factor (CDD-<br>ANF) mRNA, complete cds | 626 | 527G>T | 3    |
| M30262 | M30262 | 600295 | GEN-WA | Human cardiolipin-atrial<br>natriuretic factor (CDD-<br>ANF) mRNA, complete cds | 626 | 527G>T | 3    |
| M30262 | M30262 | 600295 | GEN-WA | Human cardiolipin-atrial<br>natriuretic factor (CDD-<br>ANF) mRNA, complete cds | 640 | 541T>C | 3    |

|        |        |        |         |                                                                                              |      |         |       |
|--------|--------|--------|---------|----------------------------------------------------------------------------------------------|------|---------|-------|
| M30262 | M30262 | 600295 | GEN-WA  | ANF) mRNA, complete cds                                                                      | 640  | 541T>C  | 3     |
|        |        |        |         | Human cardiolipin-atrial natriuretic factor (CDD-ANF) mRNA, complete cds                     |      |         |       |
| M31145 | M31145 | 146730 | GEN-3J  | Insulin-like growth factor binding protein 1 precursor                                       | 923  | 759A>G  | 1253M |
| M31145 | M31145 | 146730 | GEN-3J  | Insulin-like growth factor binding protein 1 precursor                                       | 1048 | 884T>C  | 3     |
| M31145 | M31145 | 146730 | GEN-3J  | Insulin-like growth factor binding protein 1 precursor                                       | 1260 | 1096C>G | 3     |
| M31159 | M31159 | 146732 | GEN-2GD | Human growth hormone-dependent insulin-like growth factor-binding protein mRNA, complete cds | 204  | 95G>C   | G32A  |
| M31159 | M31159 | 146732 | GEN-2GD | Human growth hormone-dependent insulin-like growth factor-binding protein mRNA, complete cds | 2178 | 2069A>T | 3     |
| M31328 | M31328 | 139130 | GEN-7G  | Guanine nucleotide binding protein (G protein), beta polypeptide 3                           | 1049 | 1043G>A | 3     |
| M32313 | M32313 | 184753 | GEN-5Y  | Steroid 5 alpha reductase 1                                                                  | 1271 | 1241C>T | 3     |
| M32313 | M32313 | 184753 | GEN-5Y  | Steroid 5 alpha reductase 1                                                                  | 1344 | 1314G>A | 3     |
| M32313 | M32313 | 184753 | GEN-5Y  | Steroid 5 alpha reductase 1                                                                  | 1489 | 1459G>A | 3     |
| M32313 | M32313 | 184753 | GEN-5Y  | Steroid 5 alpha reductase 1                                                                  | 1780 | 1750T>C | 3     |
| M34479 | M34479 | 179060 | GEN-F9  | Pyruvate dehydrogenase (lipoamide) beta                                                      | 109  | 109G>A  | D37N  |
| M34479 | M34479 | 179060 | GEN-F9  | Pyruvate dehydrogenase (lipoamide) beta                                                      | 438  | 438A>G  | S     |
| M34479 | M34479 | 179060 | GEN-F9  | Pyruvate dehydrogenase (lipoamide) beta                                                      | 1172 | 1172A>C | 3     |
| M34479 | M34479 | 179060 | GEN-F9  | Pyruvate dehydrogenase (lipoamide) beta                                                      | 1179 | 1179C>T | 3     |
| M34479 | M34479 | 179060 | GEN-F9  | Pyruvate dehydrogenase (lipoamide) beta                                                      | 1323 | 1323C>A | 3     |

|        |        |        |         |                                                                                                                 |      |         |       |
|--------|--------|--------|---------|-----------------------------------------------------------------------------------------------------------------|------|---------|-------|
| M34479 | M34479 | 179060 | GEN-F9  | Pyruvate dehydrogenase (lipoamide) beta                                                                         | 1376 | 1376G>C | 3     |
| M34479 | M34479 | 179060 | GEN-F9  | Pyruvate dehydrogenase (lipoamide) beta                                                                         | 1433 | 1433C>T | 3     |
| M34720 | M34720 | 103880 | GEN-RH  | aldose reductase                                                                                                | 676  | 663C>A  | S     |
| M34720 | M34720 | 103880 | GEN-RH  | aldose reductase                                                                                                | 1176 | 1163C>A | 3     |
| M37825 | M37825 | 165190 | GEN-20M | Human fibroblast growth factor-5 (FGF-5) mRNA, complete cds                                                     | 787  | 648T>G  | S     |
| M54968 | M54968 | 190070 | GEN-35G | Human K-ras oncogene protein mRNA, complete cds                                                                 | 711  | 519T>C  | S     |
| M54968 | M54968 | 190070 | GEN-35G | Human K-ras oncogene protein mRNA, complete cds                                                                 | 936  | 744G>T  | 3     |
| M54968 | M54968 | 190070 | GEN-35G | Human K-ras oncogene protein mRNA, complete cds                                                                 | 1270 | 1078T>C | 3     |
| M54968 | M54968 | 190070 | GEN-35G | Human K-ras oncogene protein mRNA, complete cds                                                                 | 3268 | 3076T>G | 3     |
| M54968 | M54968 | 190070 | GEN-35G | Human K-ras oncogene protein mRNA, complete cds                                                                 | 4529 | 4337A>C | 3     |
| M54968 | M54968 | 190070 | GEN-35G | Human K-ras oncogene protein mRNA, complete cds                                                                 | 4555 | 4363A>G | 3     |
| M54968 | M54968 | 190070 | GEN-35G | Human K-ras oncogene protein mRNA, complete cds                                                                 | 4672 | 4480A>C | 3     |
| M55531 | M55531 | 138230 | GEN-FF  | Solute carrier family 2 (facilitated glucose transporter), member 5                                             | 1208 | 1133T>G | V378G |
| M55531 | M55531 | 138230 | GEN-FF  | Solute carrier family 2 (facilitated glucose transporter), member 5                                             | 1975 | 1900C>T | 3     |
| M55531 | M55531 | 138230 | GEN-FF  | Solute carrier family 2 (facilitated glucose transporter), member 5                                             | 1985 | 1910A>G | 3     |
| M57899 | M57899 | 191740 | GEN-38A | Solute carrier family 2 (facilitated glucose transporter), member 5 Human bilirubin UDP-glucuronosyltransferase | 1828 | 1813C>T | 3     |

|        |        |        |         |                                                                                                          |      |                       |       |
|--------|--------|--------|---------|----------------------------------------------------------------------------------------------------------|------|-----------------------|-------|
| M57899 | M57899 | 191740 | GEN-38A | isozyme 1 mRNA, complete cds<br>Human bilirubin UDP-glucuronosyltransferase isozyme 1 mRNA, complete cds | 1956 | 1941C>G               | 3     |
| M57899 | M57899 | 191740 | GEN-38A | Human bilirubin UDP-glucuronosyltransferase isozyme 1 mRNA, complete cds                                 | 2057 | 2042C>G               | 3     |
| M59305 | M59305 | 108962 | GEN-39P | Human atrial natriuretic peptide clearance receptor (ANP C-receptor) mRNA, complete cds                  | 160  | (-203)-(-199)delTTTTT | F     |
| M59830 | M59830 | 603012 | GEN-MSB | Human MHC class III HSP70-2 gene (HLA), complete cds                                                     | 1860 | 1860C>G               | S     |
| M61906 | M61906 | 171833 | GEN-RV  | Human P13-kinase associated p85 mRNA sequence                                                            | 3112 | 3113A>G               | 3     |
| M62782 | M62782 | 146734 | GEN-3CU | Homo sapiens insulin-like growth factor binding protein 5 (IGFBP-5) mRNA, complete cds                   | 908  | 852C>T                | 3     |
| M63960 | M63960 | 176875 | GEN-FT  | Protein phosphatase 1, catalytic subunit, alpha isoform                                                  | 1087 | 1058G>T               | 3     |
| M63960 | M63960 | 176875 | GEN-FT  | Protein phosphatase 1, catalytic subunit, alpha isoform                                                  | 1292 | 1263G>A               | 3     |
| M64590 | M64590 | 238300 | GEN-FU  | Glycine cleavage system: Protein P                                                                       | 3076 | 2926A>G               | M976V |
| M64710 | M64710 | None   | GEN-KUW | Human C-type natriuretic peptide gene, complete cds                                                      | 199  | 200C>G                | 3     |
| M64710 | M64710 | None   | GEN-KUW | Human C-type natriuretic peptide gene, complete cds                                                      | 777  | 778G>A                | 3     |
| M64710 | M64710 | None   | GEN-KUW | Human C-type natriuretic peptide gene, complete cds                                                      | 1215 | 1216A>G               | 3     |

|        |        |        |         |                                                                                                       |      |         |       |
|--------|--------|--------|---------|-------------------------------------------------------------------------------------------------------|------|---------|-------|
| M65028 | M65028 | 602372 | GEN-3FM | Human hnRNP type A/B protein mRNA, complete cds                                                       | 273  | 131C>G  | P44R  |
| M65028 | M65028 | 602372 | GEN-3FM | Human hnRNP type A/B protein mRNA, complete cds                                                       | 595  | 453C>G  | S     |
| M65028 | M65028 | 602372 | GEN-3FM | Human hnRNP type A/B protein mRNA, complete cds                                                       | 1255 | 1113A>G | 3     |
| M68867 | M68867 | 180231 | GEN-S1  | Human cellular retinoic acid-binding protein II (CRABP) mRNA, complete cds                            | 604  | 506C>A  | 3     |
| M82962 | M82962 | 600388 | GEN-3XC | Human N-benzoyl-L-tyrosyl-p-amino-benzoic acid hydrolase alpha subunit (PPH alpha) mRNA, complete cds | 2316 | 2307T>G | 3     |
| M82962 | M82962 | 600388 | GEN-3XC | Human N-benzoyl-L-tyrosyl-p-amino-benzoic acid hydrolase alpha subunit (PPH alpha) mRNA, complete cds | 2428 | 2419A>C | 3     |
| M83667 | M83667 | 116898 | GEN-3YG | Human NF-IL6-beta protein mRNA, complete cds                                                          | 574  | 486G>T  | E162D |
| M83667 | M83667 | 116898 | GEN-3YG | Human NF-IL6-beta protein mRNA, complete cds                                                          | 578  | 490C>T  | P164S |
| M83667 | M83667 | 116898 | GEN-3YG | Human NF-IL6-beta protein mRNA, complete cds                                                          | 581  | 493C>T  | R165C |
| M83667 | M83667 | 116898 | GEN-3YG | Human NF-IL6-beta protein mRNA, complete cds                                                          | 974  | 886C>G  | 3     |
| M84755 | M84755 | 162641 | GEN-46  | Neuropeptide Y1                                                                                       | 1121 | 1121A>C | K374T |
| M86553 | M86553 | 116845 | GEN-416 | Human cathepsin S mRNA, complete cds                                                                  | 26   | 20T>C   | V7A   |
| M86553 | M86553 | 116845 | GEN-416 | Human cathepsin S mRNA, complete cds                                                                  | 487  | 481A>T  | T161S |
| M86553 | M86553 | 116845 | GEN-416 | Human cathepsin S mRNA, complete cds                                                                  | 705  | 699G>C  | S     |

|        |        |        |         |                                                   |      |          |       |
|--------|--------|--------|---------|---------------------------------------------------|------|----------|-------|
| M86553 | M86553 | 116845 | GEN-416 | mRNA, complete cds                                | 1149 | 1143T>G  | 3     |
|        |        |        |         | Human cathepsin S                                 |      |          |       |
| M87290 | M87290 | 106165 | GEN-19  | mRNA, complete cds                                | 296  | 16T>C    | S6P   |
| M87290 | M87290 | 106165 | GEN-19  | Angiotensin receptor AT1                          | 413  | 133G>A   | G45R  |
| M87290 | M87290 | 106165 | GEN-19  | Angiotensin receptor AT1                          | 853  | 573T>C   | S     |
| M87290 | M87290 | 106165 | GEN-19  | Angiotensin receptor AT1                          | 853  | 573T>C   | S     |
| M87290 | M87290 | 106165 | GEN-19  | Angiotensin receptor AT1                          | 1342 | 1062A>G  | S     |
| M87290 | M87290 | 106165 | GEN-19  | Angiotensin receptor AT1                          | 1342 | 1062A>G  | S     |
| M87290 | M87290 | 106165 | GEN-19  | Angiotensin receptor AT1                          | 1430 | 1150T>G  | 3     |
| M87290 | M87290 | 106165 | GEN-19  | Angiotensin receptor AT1                          | 1446 | 1166C>A  | 3     |
| M87290 | M87290 | 106165 | GEN-19  | Angiotensin receptor AT1                          | 1446 | 1166C>A  | 3     |
| M87290 | M87290 | 106165 | GEN-19  | Angiotensin receptor AT1                          | 1446 | 1166C>A  | 3     |
| M87290 | M87290 | 106165 | GEN-19  | Angiotensin receptor AT1                          | 1453 | 1173A>G  | 3     |
| M87290 | M87290 | 106165 | GEN-19  | Angiotensin receptor AT1                          | 1677 | 1397G>A  | 3     |
| M87290 | M87290 | 106165 | GEN-19  | Angiotensin receptor AT1                          | 1797 | 1517G>T  | 3     |
| M87290 | M87290 | 106165 | GEN-19  | Angiotensin receptor AT1                          | 1885 | 1605C>T  | 3     |
| M87290 | M87290 | 106165 | GEN-19  | Angiotensin receptor AT1                          | 1916 | 1636T>C  | 3     |
| M87290 | M87290 | 106165 | GEN-19  | Angiotensin receptor AT1                          | 2158 | 1878A>G  | 3     |
| M90516 | M90516 | 138292 | GEN-GI  | Glutamine-fructose-6-phosphate transaminase       | 2968 | 2846T>G  | 3     |
| M93415 | M93415 | 102581 | GEN-48S | Human activin type II receptor mRNA, complete cds | 136  | (-38)G>T | 5     |
| MC1R   | X67594 | 155555 | GEN-4G4 | H.sapiens mRNA for MSH receptor                   | 346  | 178G>T   | V60L  |
| MC1R   | X67594 | 155555 | GEN-4G4 | H.sapiens mRNA for MSH receptor                   | 656  | 488A>G   | Q163R |
| MC1R   | X67594 | 155555 | GEN-4G4 | H.sapiens mRNA for MSH receptor                   | 1068 | 900C>T   | S     |
| MC1R   | X67594 | 155555 | GEN-4G4 | H.sapiens mRNA for MSH receptor                   | 1110 | 942A>G   | S     |
| MC1R   | X67594 | 155555 | GEN-4G4 | H.sapiens mRNA for MSH receptor                   | 1134 | 966G>A   | 3     |
| MET    | M35074 | 164860 | GEN-2LU | Human met oncogene mRNA, 3 end                    | 60   | 60C>T    | S     |
| MET    | M35074 | 164860 | GEN-2LU | Human met oncogene mRNA, 3 end                    | 294  | 294G>A   | S     |



|       |        |        |         |                                                                |      |         |       |
|-------|--------|--------|---------|----------------------------------------------------------------|------|---------|-------|
| MGP   | M58549 | 154870 | GEN-38Y | Human matrix Gla protein (MGP) mRNA, complete cds              | 330  | 304A>G  | T102A |
| MMP12 | L23808 | 601046 | GEN-27J | Human metalloproteinase (HME) mRNA, complete cds               | 1082 | 1070A>G | N357S |
| MMP2  | D85510 | 602261 | GEN-40A | Homo sapiens mRNA for SMCP-2, partial cds                      | 2389 | 2389G>C | 3     |
| MPV17 | X76538 | 600945 | GEN-3P6 | H.sapiens Mpv17 mRNA                                           | 575  | 548C>T  | 3     |
| MTP   | X75500 | 157147 | GEN-3O7 | H.sapiens mRNA for microsomal triglyceride transfer protein    | 1847 | 1823T>G | F608C |
| MTP   | X75500 | 157147 | GEN-3O7 | H.sapiens mRNA for microsomal triglyceride transfer protein    | 3231 | 3207G>A | 3     |
| NGFB  | X52599 | 162030 | GEN-33V | Human mRNA for beta nerve growth factor                        | 832  | 663G>A  | S     |
| NGFR  | M14764 | 162010 | GEN-1S8 | Human nerve growth factor receptor mRNA, complete cds          | 2716 | 2603C>T | 3     |
| NGFR  | M14764 | 162010 | GEN-1S8 | Human nerve growth factor receptor mRNA, complete cds          | 2729 | 2616C>T | 3     |
| NGFR  | M14764 | 162010 | GEN-1S8 | Human nerve growth factor receptor mRNA, complete cds          | 2912 | 2799G>A | 3     |
| NGFR  | M14764 | 162010 | GEN-1S8 | Human nerve growth factor receptor mRNA, complete cds          | 3252 | 3139C>G | 3     |
| NOS1  | U17327 | 163731 | GEN-209 | Human neuronal nitric oxide synthase (NOS1) mRNA, complete cds | 3391 | 2706C>T | S     |
| NOS2A | X73029 | 163730 | GEN-3LW | H.sapiens mRNA for nitric oxide synthase                       | 1380 | 1155C>T | S     |
| NOS2A | X73029 | 163730 | GEN-3LW | H.sapiens mRNA for nitric oxide synthase                       | 1380 | 1155C>T | S     |
| NOS2A | X73029 | 163730 | GEN-3LW | H.sapiens mRNA for nitric oxide synthase                       | 1503 | 1278C>T | S     |
| NOS2A | X73029 | 163730 | GEN-3LW | H.sapiens mRNA for nitric oxide synthase                       | 1503 | 1278C>T | S     |

|       |        |        |         |                                          |      |           |       |
|-------|--------|--------|---------|------------------------------------------|------|-----------|-------|
| NOS2A | X73029 | 163730 | GEN-3LW | H.sapiens mRNA for nitric oxide synthase | 2048 | 1823C>T   | S608L |
| NOS2A | X73029 | 163730 | GEN-3LW | H.sapiens mRNA for nitric oxide synthase | 2048 | 1823C>T   | S608L |
| NOS2A | X73029 | 163730 | GEN-3LW | H.sapiens mRNA for nitric oxide synthase | 2287 | 2062G>A   | G688S |
| NOS2A | X73029 | 163730 | GEN-3LW | H.sapiens mRNA for nitric oxide synthase | 2287 | 2062G>A   | G688S |
| NOS2A | X73029 | 163730 | GEN-3LW | H.sapiens mRNA for nitric oxide synthase | 2339 | 2114A>G   | D705G |
| NOS2A | X73029 | 163730 | GEN-3LW | H.sapiens mRNA for nitric oxide synthase | 2339 | 2114A>G   | D705G |
| NOS2A | X73029 | 163730 | GEN-3LW | H.sapiens mRNA for nitric oxide synthase | 2583 | 2358T>C   | S     |
| NOS2A | X73029 | 163730 | GEN-3LW | H.sapiens mRNA for nitric oxide synthase | 2583 | 2358T>C   | S     |
| NOS2A | X73029 | 163730 | GEN-3LW | H.sapiens mRNA for nitric oxide synthase | 2982 | 2757A>G   | S     |
| NOS2A | X73029 | 163730 | GEN-3LW | H.sapiens mRNA for nitric oxide synthase | 2982 | 2757A>G   | S     |
| NOS2A | X73029 | 163730 | GEN-3LW | H.sapiens mRNA for nitric oxide synthase | 3022 | 2797C>G   | R933G |
| NOS2A | X73029 | 163730 | GEN-3LW | H.sapiens mRNA for nitric oxide synthase | 3022 | 2797C>G   | R933G |
| NOS2A | X73029 | 163730 | GEN-3LW | H.sapiens mRNA for nitric oxide synthase | 3051 | 2826C>T   | S     |
| NOS2A | X73029 | 163730 | GEN-3LW | H.sapiens mRNA for nitric oxide synthase | 3051 | 2826C>T   | S     |
| NOS2A | X73029 | 163730 | GEN-3LW | H.sapiens mRNA for nitric oxide synthase | 3693 | 3468T>C   | 3     |
| NOS2A | X73029 | 163730 | GEN-3LW | H.sapiens mRNA for nitric oxide synthase | 3693 | 3468T>C   | 3     |
| NOS2A | X73029 | 163730 | GEN-3LW | H.sapiens mRNA for nitric oxide synthase | 3715 | 3490G>A   | 3     |
| NOS2A | X73029 | 163730 | GEN-3LW | H.sapiens mRNA for nitric oxide synthase | 3715 | 3490G>A   | 3     |
| NRAS  | X02751 | 164790 | GEN-XG  | Human N-ras mRNA and flanking regions    | 221  | (-506)A>G | 5     |
| NRAS  | X02751 | 164790 | GEN-XG  | Human N-ras mRNA and flanking regions    | 390  | (-337)C>A | 5     |
| NTRK1 | X66397 | 191315 | GEN-    | H.sapiens tpr mRNA                       | 2632 | 2335G>A   | V779I |

|       |        |        |                    |                                                                      |      |           |       |
|-------|--------|--------|--------------------|----------------------------------------------------------------------|------|-----------|-------|
| NTRK3 | U05012 | 191316 | 3GN<br>GEN-<br>16V | Human receptor tyrosine<br>kinase TrkC (NTRK3)<br>mRNA, complete cds | 364  | 209G>A    | S70N  |
| NTRK3 | U05012 | 191316 | GEN-<br>16V        | Human receptor tyrosine<br>kinase TrkC (NTRK3)<br>mRNA, complete cds | 728  | 573C>T    | S     |
| NTRK3 | U05012 | 191316 | GEN-<br>16V        | Human receptor tyrosine<br>kinase TrkC (NTRK3)<br>mRNA, complete cds | 1613 | 1458C>T   | S     |
| NTRK3 | U05012 | 191316 | GEN-<br>16V        | Human receptor tyrosine<br>kinase TrkC (NTRK3)<br>mRNA, complete cds | 1643 | 1488G>C   | S     |
| OSBP  | M86917 | 167040 | GEN-425            | Human oxysterol-binding<br>protein (OSBP) mRNA,<br>complete cds      | 216  | (-265)T>G | 5     |
| OSBP  | M86917 | 167040 | GEN-425            | Human oxysterol-binding<br>protein (OSBP) mRNA,<br>complete cds      | 802  | 322C>T    | F     |
| OSBP  | M86917 | 167040 | GEN-425            | Human oxysterol-binding<br>protein (OSBP) mRNA,<br>complete cds      | 888  | 408C>T    | S     |
| OSBP  | M86917 | 167040 | GEN-425            | Human oxysterol-binding<br>protein (OSBP) mRNA,<br>complete cds      | 934  | 454T>G    | S152A |
| PACE  | X17094 | 136950 | GEN-<br>1ZV        | Human fur mRNA for furin                                             | 399  | 183C>T    | S     |
| PACE  | X17094 | 136950 | GEN-<br>1ZV        | Human fur mRNA for furin                                             | 1692 | 1476C>T   | S     |
| PACE  | X17094 | 136950 | GEN-<br>1ZV        | Human fur mRNA for furin                                             | 2067 | 1851C>G   | S     |
| PACE  | X17094 | 136950 | GEN-<br>1ZV        | Human fur mRNA for furin                                             | 2725 | 2509T>C   | 3     |
| PACE  | X17094 | 136950 | GEN-<br>1ZV        | Human fur mRNA for furin                                             | 2855 | 2639C>A   | 3     |
| PACE  | X17094 | 136950 | GEN-<br>1ZV        | Human fur mRNA for furin                                             | 2988 | 2772G>A   | 3     |
| PACE  | X17094 | 136950 | GEN-<br>1ZV        | Human fur mRNA for furin                                             | 3234 | 3018C>T   | 3     |
| PACE  | X17094 | 136950 | GEN-<br>1ZV        | Human fur mRNA for furin                                             | 3625 | 3409A>G   | 3     |

|       |        |        |         |                                                                                               |      |         |       |
|-------|--------|--------|---------|-----------------------------------------------------------------------------------------------|------|---------|-------|
| PACE  | X17094 | 136950 | GEN-1ZV | Human fur mRNA for furin                                                                      | 3883 | 3667C>T | 3     |
| PACE  | X17094 | 136950 | GEN-1ZV | Human fur mRNA for furin                                                                      | 4053 | 3837A>G | 3     |
| PAM   | M37721 | 170270 | GEN-2OK | Human peptidylglycine alpha-amidating monooxygenase mRNA, complete cds                        | 3183 | 2995T>A | 3     |
| PAM   | M37721 | 170270 | GEN-2OK | Human peptidylglycine alpha-amidating monooxygenase mRNA, complete cds                        | 3530 | 3342A>G | 3     |
| PAX6  | M77844 | 106210 | GEN-3QG | H.sapiens oculorhombin (aniridia) mRNA, complete cds                                          | 669  | 307C>T  | F     |
| PC    | U04641 | 266150 | GEN-150 | Human pyruvate carboxylase (PC) mRNA, complete cds                                            | 1391 | 1353C>T | S     |
| PC    | U04641 | 266150 | GEN-150 | Human pyruvate carboxylase (PC) mRNA, complete cds                                            | 2219 | 2181C>T | S     |
| PC    | U04641 | 266150 | GEN-150 | Human pyruvate carboxylase (PC) mRNA, complete cds                                            | 2912 | 2874G>T | S     |
| PC    | U04641 | 266150 | GEN-150 | Human pyruvate carboxylase (PC) mRNA, complete cds                                            | 3897 | 3859C>T | 3     |
| PCK1  | L05144 | 261680 | GEN-172 | Homo sapiens (clone lamda-hPEC-3) phosphoenolpyruvate carboxykinase (PCK1) mRNA, complete cds | 1223 | 1102G>A | V368I |
| PDHA1 | X52709 | 312170 | GEN-33Y | Human mRNA for brain pyruvate dehydrogenase (EC 1.2.4.1)                                      | 849  | 795A>G  | S     |
| PDHA1 | X52709 | 312170 | GEN-33Y | Human mRNA for brain pyruvate dehydrogenase (EC 1.2.4.1)                                      | 1337 | 1283C>T | 3     |
| PDHA1 | X52709 | 312170 | GEN-33Y | Human mRNA for brain pyruvate dehydrogenase (EC 1.2.4.1)                                      | 1416 | 1362G>A | 3     |

|       |        |        |         |                                                                                                          |      |         |       |
|-------|--------|--------|---------|----------------------------------------------------------------------------------------------------------|------|---------|-------|
| PEDF  | M90439 | 172860 | GEN-46E | Human molecular marker (EPC-1) gene, complete cds                                                        | 40   | 2T>C    | F     |
| PEDF  | M90439 | 172860 | GEN-46E | Human molecular marker (EPC-1) gene, complete cds                                                        | 215  | 177T>C  | S     |
| PEDF  | M90439 | 172860 | GEN-46E | Human molecular marker (EPC-1) gene, complete cds                                                        | 788  | 750C>T  | S     |
| PEDF  | M90439 | 172860 | GEN-46E | Human molecular marker (EPC-1) gene, complete cds                                                        | 900  | 862C>G  | R288G |
| PEDF  | M90439 | 172860 | GEN-46E | Human molecular marker (EPC-1) gene, complete cds                                                        | 952  | 914G>T  | G305V |
| PHKG2 | M31606 | 172471 | GEN-2H7 | Human phosphorylase kinase (PSK-C3) mRNA, complete cds                                                   | 1155 | 1062C>G | S     |
| PNLIP | M93285 | 246600 | GEN-48N | Pancreatic lipase (PNLIP) (Dietary supplement)                                                           | 646  | 646G>T  | V216L |
| POMC  | M28636 | 176830 | GEN-2DG | Adrenocorticotrophic hormone (ACTH)                                                                      | 92   | 92C>T   | 3     |
| PREP  | X74496 | 600400 | GEN-3N8 | Prolyl Endopeptidase                                                                                     | 390  | 390T>C  | S     |
| PREP  | X74496 | 600400 | GEN-3N8 | Prolyl Endopeptidase                                                                                     | 1051 | 1051T>G | L351V |
| PREP  | X74496 | 600400 | GEN-3N8 | Prolyl Endopeptidase                                                                                     | 1125 | 1125C>T | S     |
| PREP  | X74496 | 600400 | GEN-3N8 | Prolyl Endopeptidase                                                                                     | 1363 | 1363G>A | V455M |
| PTHLH | J03580 | 168470 | GEN-11U | Human, parathyroid-like protein (associated with humoral hypercalcemia of malignancy) mRNA, complete cds | 975  | 37G>A   | V13M  |
| PTHLH | J03580 | 168470 | GEN-11U | Human, parathyroid-like protein (associated with humoral hypercalcemia of malignancy) mRNA, complete cds | 996  | 58G>A   | V20M  |
| PTPRF | Y00815 | 179590 | GEN-UH  | Human mRNA for LCA-                                                                                      | 6939 | 6569A>G | 3     |

|        |        |        |             |                                                                                                                    |      |         |       |
|--------|--------|--------|-------------|--------------------------------------------------------------------------------------------------------------------|------|---------|-------|
| PYGB   | J03544 | 138550 | GEN-11L     | homolog. LAR protein<br>(leukocyte antigen related)<br>Human brain glycogen<br>phosphorylase mRNA,<br>complete cds | 718  | 639C>T  | S     |
| PYGB   | J03544 | 138550 | GEN-11L     | Human brain glycogen<br>phosphorylase mRNA,<br>complete cds                                                        | 2449 | 2370G>A | S     |
| PYGB   | J03544 | 138550 | GEN-11L     | Human brain glycogen<br>phosphorylase mRNA,<br>complete cds                                                        | 2712 | 2633C>G | 3     |
| PYGB   | J03544 | 138550 | GEN-11L     | Human brain glycogen<br>phosphorylase mRNA,<br>complete cds                                                        | 3346 | 3267C>T | 3     |
| PYGB   | J03544 | 138550 | GEN-11L     | Human brain glycogen<br>phosphorylase mRNA,<br>complete cds                                                        | 3644 | 3565G>A | 3     |
| PYGB   | J03544 | 138550 | GEN-11L     | Human brain glycogen<br>phosphorylase mRNA,<br>complete cds                                                        | 3687 | 3608G>A | 3     |
| PYGB   | J03544 | 138550 | GEN-11L     | Human brain glycogen<br>phosphorylase mRNA,<br>complete cds                                                        | 3770 | 3691G>A | 3     |
| PYGL   | M36807 | 232700 | GEN-<br>2NJ | Human liver glycogen<br>phosphorylase type IV<br>mRNA, 3 end                                                       | 702  | 702G>C  | R234S |
| PYGL   | M36807 | 232700 | GEN-<br>2NJ | Human liver glycogen<br>phosphorylase type IV<br>mRNA, 3 end                                                       | 1108 | 1108C>G | 3     |
| RAF1   | X06409 | 164760 | GEN-<br>19K | Human mRNA fragment for<br>activated c-raf-1 (exons 8-<br>17)                                                      | 486  | 487T>C  | 3     |
| RAF1   | X06409 | 164760 | GEN-<br>19K | Human mRNA fragment for<br>activated c-raf-1 (exons 8-<br>17)                                                      | 1947 | 1948C>T | 3     |
| RAF1   | X06409 | 164760 | GEN-<br>19K | Human mRNA fragment for<br>activated c-raf-1 (exons 8-<br>17)                                                      | 1992 | 1993C>A | 3     |
| S63912 | S63912 | 601233 | GEN-<br>3EJ | D10S102=FBRNP [human,<br>fetal brain, mRNA, 3043 nt]                                                               | 2193 | 2163G>A | 3     |
| S70154 | S70154 | 100678 | GEN-GY      | ACAT2                                                                                                              | 669  | 632A>G  | K211R |

|        |        |        |             |                                                                           |      |                      |       |
|--------|--------|--------|-------------|---------------------------------------------------------------------------|------|----------------------|-------|
| S70154 | S70154 | 100678 | GEN-GY      | ACAT2                                                                     | 820  | 783T>C               | S     |
| S70154 | S70154 | 100678 | GEN-GY      | ACAT2                                                                     | 820  | 783T>C               | S     |
| S70154 | S70154 | 100678 | GEN-GY      | ACAT2                                                                     | 856  | 819G>A               | S     |
| S70154 | S70154 | 100678 | GEN-GY      | ACAT2                                                                     | 856  | 819G>A               | S     |
| S70154 | S70154 | 100678 | GEN-GY      | ACAT2                                                                     | 1388 | 1351T>G              | 3     |
| S70154 | S70154 | 100678 | GEN-GY      | ACAT2                                                                     | 1395 | 1358-<br>1362CTTTA>  | 3     |
| S70154 | S70154 | 100678 | GEN-GY      | ACAT2                                                                     | 1395 | CTTTA                | F     |
| S70154 | S70154 | 100678 | GEN-GY      | ACAT2                                                                     | 1395 | 1358-<br>1362delCTTT | F     |
| S70154 | S70154 | 100678 | GEN-GY      | ACAT2                                                                     | 1419 | A                    | 3     |
| S70154 | S70154 | 100678 | GEN-GY      | ACAT2                                                                     | 1419 | 1382C>A              | 3     |
| S74445 | S74445 | 180230 | GEN-<br>3N7 | cellular retinoic acid-<br>binding protein [human,<br>skin, mRNA, 735 nt] | 134  | 60G>C                | S     |
| SLC5A1 | M24847 | 182380 | GEN-<br>28S | Human Na <sup>+</sup> /glucose<br>cotransporter 1 mRNA,<br>complete cds   | 2226 | 2216C>T              | 3     |
| SLO    | U02632 | 600150 | GEN-XA      | Calcium-activated<br>potassium channel                                    | 2377 | 2377T>G              | S793A |
| SOD2   | X07834 | 147460 | GEN-<br>1ES | Human mRNA for<br>manganese superoxide<br>dismutase (EC 1.15.1.1)         | 44   | 40C>G                | P14A  |
| SOD2   | X07834 | 147460 | GEN-<br>1ES | Human mRNA for<br>manganese superoxide<br>dismutase (EC 1.15.1.1)         | 51   | 47T>C                | V16A  |
| SOD2   | X07834 | 147460 | GEN-<br>1ES | Human mRNA for<br>manganese superoxide<br>dismutase (EC 1.15.1.1)         | 198  | 194C>A               | T65N  |
| SOD2   | X07834 | 147460 | GEN-<br>1ES | Human mRNA for<br>manganese superoxide<br>dismutase (EC 1.15.1.1)         | 249  | 245T>C               | I82T  |
| SORD   | U07361 | 182500 | GEN-<br>1DR | Homo sapiens sorbitol<br>dehydrogenase gene,<br>complete cds              | 606  | 465C>T               | S     |
| SORD   | U07361 | 182500 | GEN-<br>1DR | Homo sapiens sorbitol<br>dehydrogenase gene,<br>complete cds              | 857  | 716A>T               | Q239L |
| SORD   | U07361 | 182500 | GEN-        | Homo sapiens sorbitol<br>dehydrogenase gene,<br>complete cds              | 1247 | 1106T>C              | 3     |

|       |        |        |         |        |                                            |      |         |       |
|-------|--------|--------|---------|--------|--------------------------------------------|------|---------|-------|
| SORD  | U07361 | 182500 | GEN-1DR | 1DR    | dehydrogenase gene, complete cds           | 1275 | 1134T>G | 3     |
| SPARC | J03040 | 182120 | GEN-ZC  | GEN-ZC | Human SPARC/osteonectin mRNA, complete cds | 70   | 13A>T   | I5F   |
| SPARC | J03040 | 182120 | GEN-ZC  | GEN-ZC | Human SPARC/osteonectin mRNA, complete cds | 123  | 66A>G   | S     |
| SPARC | J03040 | 182120 | GEN-ZC  | GEN-ZC | Human SPARC/osteonectin mRNA, complete cds | 184  | 127G>T  | V43L  |
| SPARC | J03040 | 182120 | GEN-ZC  | GEN-ZC | Human SPARC/osteonectin mRNA, complete cds | 559  | 502C>G  | R168G |
| SPARC | J03040 | 182120 | GEN-ZC  | GEN-ZC | Human SPARC/osteonectin mRNA, complete cds | 998  | 941C>G  | 3     |
| SPARC | J03040 | 182120 | GEN-ZC  | GEN-ZC | Human SPARC/osteonectin mRNA, complete cds | 1183 | 1126C>G | 3     |
| SPARC | J03040 | 182120 | GEN-ZC  | GEN-ZC | Human SPARC/osteonectin mRNA, complete cds | 1413 | 1356G>A | 3     |
| SPARC | J03040 | 182120 | GEN-ZC  | GEN-ZC | Human SPARC/osteonectin mRNA, complete cds | 1551 | 1494C>G | 3     |
| SPARC | J03040 | 182120 | GEN-ZC  | GEN-ZC | Human SPARC/osteonectin mRNA, complete cds | 1922 | 1865G>T | 3     |
| SPARC | J03040 | 182120 | GEN-ZC  | GEN-ZC | Human SPARC/osteonectin mRNA, complete cds | 2072 | 2015T>C | 3     |
| SPARC | J03040 | 182120 | GEN-ZC  | GEN-ZC | Human SPARC/osteonectin mRNA, complete cds | 2092 | 2035A>G | 3     |
| SPARC | J03040 | 182120 | GEN-ZC  | GEN-ZC | Human SPARC/osteonectin mRNA, complete cds | 2104 | 2047A>C | 3     |



|        |        |        |         |                                                                        |      |         |       |
|--------|--------|--------|---------|------------------------------------------------------------------------|------|---------|-------|
| SPP1   | X13694 | 166490 | GEN-1P2 | Human mRNA for osteopontin                                             | 349  | 282T>C  | S     |
| SPP1   | X13694 | 166490 | GEN-1P2 | Human mRNA for osteopontin                                             | 817  | 750C>T  | S     |
| SPP1   | X13694 | 166490 | GEN-1P2 | Human mRNA for osteopontin                                             | 969  | 902G>A  | R301H |
| SPP1   | X13694 | 166490 | GEN-1P2 | Human mRNA for osteopontin                                             | 1150 | 1083A>G | 3     |
| SPP1   | X13694 | 166490 | GEN-1P2 | Human mRNA for osteopontin                                             | 1306 | 1239A>C | 3     |
| SRD5A2 | M74047 | 264600 | GEN-CDC | Human steroid 5-alpha-reductase 2 (SRD5A2) mRNA, complete cds          | 2379 | 2352A>G | 3     |
| STAR   | U17280 | 600617 | GEN-208 | Human steroidogenic acute regulatory protein (STAR) mRNA, complete cds | 1439 | 1313C>T | 3     |
| TBG    | M14091 | 314200 | GEN-1QO | Human thyroxine-binding globulin mRNA, complete cds                    | 901  | 571G>A  | D191N |
| TBG    | M14091 | 314200 | GEN-1QO | Human thyroxine-binding globulin mRNA, complete cds                    | 1239 | 909G>T  | L303F |
| TCF14  | X76930 | 600281 | GEN-3PH | H.sapiens HNF 4 mRNA for hepatocyte nuclear factor 4                   | 1325 | 1306C>T | P436S |
| TF     | M12530 | 190000 | GEN-1MK | Human transferrin mRNA, complete cds                                   | 654  | 624G>A  | S     |
| TF     | M12530 | 190000 | GEN-1MK | Human transferrin mRNA, complete cds                                   | 768  | 738C>G  | C246W |
| TF     | M12530 | 190000 | GEN-1MK | Human transferrin mRNA, complete cds                                   | 1447 | 1417G>T | V473F |
| TF     | M12530 | 190000 | GEN-1MK | Human transferrin mRNA, complete cds                                   | 1602 | 1572G>C | S     |
| TF     | M12530 | 190000 | GEN-1MK | Human transferrin mRNA, complete cds                                   | 1632 | 1602C>T | S     |
| TF     | M12530 | 190000 | GEN-1MK | Human transferrin mRNA, complete cds                                   | 1795 | 1765C>T | P589S |
| TGFBR2 | M85079 | 190182 | GEN-3ZS | Human TGF-beta type II receptor mRNA, complete cds                     | 2045 | 1710A>C | 3     |
| TGFBR3 | L07594 | 600742 | GEN-    | Human transforming                                                     | 3966 | 3618G>C | 3     |

|        |        |        |         |     |                                                                               |      |         |       |
|--------|--------|--------|---------|-----|-------------------------------------------------------------------------------|------|---------|-------|
| U00968 | U00968 | 184756 | GEN-UU  | 1EA | growth factor-beta type III receptor (TGF-beta) mRNA, complete cds            | 3983 | 3817G>A | 3     |
| U02031 | U02031 | 600481 | GEN-WD  |     | Human SREBP-1 mRNA, complete cds                                              | 1089 | 972G>A  | S     |
| U09648 | U09648 | 600650 | GEN-1I  |     | Human sterol regulatory element binding protein-2 mRNA, complete cds          | 2556 | 2040G>A | 3     |
| U09648 | U09648 | 600650 | GEN-1I  |     | Palmitoyltransferase II                                                       | 2675 | 2159G>A | 3     |
| U09648 | U09648 | 600650 | GEN-1I  |     | Palmitoyltransferase II                                                       | 2792 | 2276G>A | 3     |
| U09648 | U09648 | 600650 | GEN-1I  |     | Palmitoyltransferase II                                                       | 2825 | 2309G>A | 3     |
| U09759 | U09759 | 602896 | GEN-1HA |     | Palmitoyltransferase II                                                       | 303  | 152A>G  | N51S  |
| U09759 | U09759 | 602896 | GEN-1HA |     | Human protein kinase (JNK2) mRNA, complete cds                                | 1079 | 928A>G  | I310V |
| U09759 | U09759 | 602896 | GEN-1HA |     | Human protein kinase (JNK2) mRNA, complete cds                                | 1280 | 1129C>T | P377S |
| U09759 | U09759 | 602896 | GEN-1HA |     | Human protein kinase (JNK2) mRNA, complete cds                                | 1559 | 1408C>T | 3     |
| U16031 | U16031 | None   | GEN-HX  |     | Transcription Factor IL-4 Stat                                                | 2964 | 2799G>A | 3     |
| U16660 | U16660 | 600696 | GEN-1YD |     | Human peroxisomal enoyl-CoA hydratase-like protein (HPXEL) mRNA, complete cds | 149  | 122A>C  | E41A  |
| U16660 | U16660 | 600696 | GEN-1YD |     | Human peroxisomal enoyl-CoA hydratase-like protein (HPXEL) mRNA, complete cds | 402  | 375G>A  | S     |
| U16660 | U16660 | 600696 | GEN-1YD |     | Human peroxisomal enoyl-CoA hydratase-like protein (HPXEL) mRNA, complete cds | 802  | 775C>G  | P259A |

|        |        |        |         |                                                                               |      |                 |       |
|--------|--------|--------|---------|-------------------------------------------------------------------------------|------|-----------------|-------|
| U16660 | U16660 | 600696 | GEN-1YD | Human peroxisomal enoyl-CoA hydratase-like protein (HPXEL) mRNA, complete cds | 1157 | 1130G>A         | 3     |
| U19775 | U19775 | 600289 | GEN-22C | Human MAP kinase Mxi2 (MXI2) mRNA, complete cds                               | 731  | 688G>A          | D230N |
| U24183 | U24183 | 232800 | GEN-19  | Phosphofructokinase, muscle                                                   | 70   | (-1204)G>A      | 5     |
| U24183 | U24183 | 232800 | GEN-19  | Phosphofructokinase, muscle                                                   | 237  | (-1037)G>A      | 5     |
| U24183 | U24183 | 232800 | GEN-19  | Phosphofructokinase, muscle                                                   | 592  | (-682)T>C       | 5     |
| U24183 | U24183 | 232800 | GEN-19  | Phosphofructokinase, muscle                                                   | 2662 | 1389T>G         | S     |
| U24183 | U24183 | 232800 | GEN-19  | Phosphofructokinase, muscle                                                   | 2953 | 1680C>T         | 3     |
| U25029 | U25029 | 138040 | GEN-82  | Glucocorticoid receptor alpha                                                 | 335  | 335C>T          | 3     |
| U25029 | U25029 | 138040 | GEN-82  | Glucocorticoid receptor alpha                                                 | 386  | 386T>C          | 3     |
| U25029 | U25029 | 138040 | GEN-82  | Glucocorticoid receptor alpha                                                 | 1069 | 1069C>T         | 3     |
| U26553 | U26553 | 114131 | GEN-66  | Calcitonin Receptor                                                           | 1412 | 1340C>T         | P447L |
| U26553 | U26553 | 114131 | GEN-66  | Calcitonin Receptor                                                           | 1515 | 1443T>C         | 3     |
| U32500 | U32500 | 162642 | GEN-1P  | Neuropeptide Y2                                                               | 407  | 159C>T          | S     |
| U32500 | U32500 | 162642 | GEN-1P  | Neuropeptide Y2                                                               | 833  | 585T>C          | S     |
| U32500 | U32500 | 162642 | GEN-1P  | Neuropeptide Y2                                                               | 833  | 585T>C          | S     |
| U32500 | U32500 | 162642 | GEN-1P  | Neuropeptide Y2                                                               | 1184 | 936T>C          | S     |
| U32500 | U32500 | 162642 | GEN-1P  | Neuropeptide Y2                                                               | 1184 | 936T>C          | S     |
| U32500 | U32500 | 162642 | GEN-1P  | Neuropeptide Y2                                                               | 1706 | 1458-1460TAT>TA | 3     |
| U32500 | U32500 | 162642 | GEN-1P  | Neuropeptide Y2                                                               | 1706 | 1458-1460delTAT | 3     |
| U32500 | U32500 | 162642 | GEN-1P  | Neuropeptide Y2                                                               | 2782 | 2534^2535ins CA | F     |
| U32989 | U32989 | 191070 | GEN-2JH | Human tryptophan oxygenase (TDO) mRNA,                                        | 991  | 927G>A          | S     |

|        |        |        |         |                                                                                 |      |         |       |
|--------|--------|--------|---------|---------------------------------------------------------------------------------|------|---------|-------|
| U40002 | U40002 | 151750 | GEN-2RH | Human hormone-sensitive lipase testicular isoform mRNA, complete cds            | 2076 | 1799C>A | P600H |
| U40347 | U40347 | 600950 | GEN-2RK | Human serotonin N-acetyltransferase mRNA, complete cds                          | 382  | 148G>A  | E50K  |
| U40396 | U40396 | 602691 | GEN-6W  | Steroid receptor coactivator (SRC-1)                                            | 285  | 229A>C  | K77Q  |
| U40396 | U40396 | 602691 | GEN-6W  | Steroid receptor coactivator (SRC-1)                                            | 314  | 258A>T  | K86N  |
| U40396 | U40396 | 602691 | GEN-6W  | Steroid receptor coactivator (SRC-1)                                            | 336  | 280C>T  | P94S  |
| U40396 | U40396 | 602691 | GEN-6W  | Steroid receptor coactivator (SRC-1)                                            | 688  | 632C>T  | T211I |
| U40396 | U40396 | 602691 | GEN-6W  | Steroid receptor coactivator (SRC-1)                                            | 970  | 914C>A  | A305E |
| U40396 | U40396 | 602691 | GEN-6W  | Steroid receptor coactivator (SRC-1)                                            | 1511 | 1455G>A | S     |
| U40396 | U40396 | 602691 | GEN-6W  | Steroid receptor coactivator (SRC-1)                                            | 2377 | 2321C>T | T774M |
| U40396 | U40396 | 602691 | GEN-6W  | Steroid receptor coactivator (SRC-1)                                            | 2730 | 2674C>T | P892S |
| U41078 | U41078 | 600754 | GEN-2SU | Human membrane-type matrix metalloproteinase-1 mRNA, complete cds               | 22   | 22C>T   | P8S   |
| U43142 | U43142 | 601528 | GEN-2UM | Human vascular endothelial growth factor related protein VRP mRNA, complete cds | 1499 | 1128C>T | S     |
| U48730 | U48730 | 601511 | GEN-JA  | Transcription Factor Stat5b                                                     | 494  | 484T>C  | S     |
| U48730 | U48730 | 601511 | GEN-JA  | Transcription Factor Stat5b                                                     | 496  | 486A>G  | S     |
| U48730 | U48730 | 601511 | GEN-JA  | Transcription Factor Stat5b                                                     | 499  | 489A>G  | S     |
| U48730 | U48730 | 601511 | GEN-JA  | Transcription Factor Stat5b                                                     | 502  | 492G>A  | S     |
| U48730 | U48730 | 601511 | GEN-JA  | Transcription Factor Stat5b                                                     | 570  | 560G>C  | G187A |
| U48730 | U48730 | 601511 | GEN-JA  | Transcription Factor Stat5b                                                     | 573  | 563C>A  | P188Q |
| U48730 | U48730 | 601511 | GEN-JA  | Transcription Factor Stat5b                                                     | 1003 | 993G>A  | S     |
| U48730 | U48730 | 601511 | GEN-JA  | Transcription Factor Stat5b                                                     | 1063 | 1053T>C | S     |
| U48730 | U48730 | 601511 | GEN-JA  | Transcription Factor Stat5b                                                     | 1066 | 1056G>A | S     |

|        |        |        |         |                                                                                                                |      |         |       |
|--------|--------|--------|---------|----------------------------------------------------------------------------------------------------------------|------|---------|-------|
| U48730 | U48730 | 601511 | GEN-JA  | Transcription Factor Stat5b                                                                                    | 1105 | 1095C>T | S     |
| U48730 | U48730 | 601511 | GEN-JA  | Transcription Factor Stat5b                                                                                    | 1159 | 1149C>T | S     |
| U48730 | U48730 | 601511 | GEN-JA  | Transcription Factor Stat5b                                                                                    | 1969 | 1959C>T | S     |
| U49516 | U49516 | 312861 | GEN-1Q  | Serotonin 5-HT receptors<br>5-HT2C                                                                             | 2915 | 2187A>C | 3     |
| U49516 | U49516 | 312861 | GEN-1Q  | Serotonin 5-HT receptors<br>5-HT2C                                                                             | 2947 | 2219A>G | 3     |
| U62768 | U62768 | 151300 | GEN-3CR | Human oxytocinase splice<br>variant 1 mRNA, complete<br>cds                                                    | 3356 | 3295G>C | 3     |
| U62768 | U62768 | 151300 | GEN-3CR | Human oxytocinase splice<br>variant 1 mRNA, complete<br>cds                                                    | 3547 | 3486C>T | 3     |
| U71321 | U71321 | 602623 | GEN-2TW | Human FK506-binding<br>protein FKBP51 mRNA,<br>complete cds                                                    | 1248 | 1095C>T | S     |
| U71321 | U71321 | 602623 | GEN-2TW | Human FK506-binding<br>protein FKBP51 mRNA,<br>complete cds                                                    | 1425 | 1272G>A | S     |
| U94357 | U94357 | None   | GEN-498 | Homo sapiens glycogenin-<br>2 delta (glycogenin-2)<br>mRNA, partial cds                                        | 1595 | 1595C>T | 3     |
| U94357 | U94357 | None   | GEN-498 | Homo sapiens glycogenin-<br>2 delta (glycogenin-2)<br>mRNA, partial cds                                        | 1844 | 1844A>C | 3     |
| UCP2   | U76367 | 601693 | GEN-3OV | Human uncoupling protein-<br>2 (UCP2) mRNA, nuclear<br>gene encoding<br>mitochondrial protein,<br>complete cds | 164  | 164C>T  | A55V  |
| V00518 | V00518 | 118850 | GEN-P4  | Human messenger RNA<br>for chorionic gonadotropin                                                              | 565  | 515T>C  | 3     |
| V00519 | V00519 | 139250 | GEN-4U  | Growth hormone 1                                                                                               | 299  | 259C>A  | P87T  |
| V00519 | V00519 | 139250 | GEN-4U  | Growth hormone 1                                                                                               | 524  | 484G>T  | G162W |
| V00566 | V00566 | 176760 | GEN-4V  | Prolactin                                                                                                      | 574  | 570G>A  | S     |
| V00571 | V00571 | 122560 | GEN-CBO | corticotropin releasing<br>factor                                                                              | 822  | 637delA | F     |
| V00571 | V00571 | 122560 | GEN-CBO | corticotropin releasing<br>factor                                                                              | 837  | 652G>A  | 3     |
| VEGF   | M32977 | 192240 | GEN-2JF | Human heparin-binding                                                                                          | 50   | (-7)C>T | 5     |

|        |        |        |         |                                                                                    |      |          |       |
|--------|--------|--------|---------|------------------------------------------------------------------------------------|------|----------|-------|
| VEGF   | M32977 | 192240 | GEN-2JF | vascular endothelial growth factor (VEGF) mRNA, complete cds                       | 92   | 36C>T    | S     |
| VLDLR  | L20470 | 192977 | GEN-23D | Human heparin-binding vascular endothelial growth factor (VEGF) mRNA, complete cds | 336  | (-56)C>T | 5     |
| VLDLR  | L20470 | 192977 | GEN-23D | Human very low density lipoprotein receptor mRNA, complete cds                     | 3566 | 3175T>C  | 3     |
| X00264 | X00264 | 152780 | GEN-CC2 | Human beta-LH gene (luteinizing hormone gene beta subunit)                         | 1015 | 1016G>C  | 3     |
| X00264 | X00264 | 152780 | GEN-CC2 | Human beta-LH gene (luteinizing hormone gene beta subunit)                         | 1033 | 1034C>A  | 3     |
| X00568 | X00568 | 207750 | GEN-6Z  | Apolipoprotein C-II                                                                | 70   | 70C>A    | Q24K  |
| X02317 | X02317 | 147450 | GEN-KM  | Superoxide dismutase 1 (Cu/Zn)                                                     | 614  | 550A>C   | 3     |
| X02812 | X02812 | 190180 | GEN-XR  | Human mRNA for transforming growth factor-beta (TGF-beta)                          | 870  | 29C>T    | P10L  |
| X02812 | X02812 | 190180 | GEN-XR  | Human mRNA for transforming growth factor-beta (TGF-beta)                          | 979  | 138C>G   | I46M  |
| X02812 | X02812 | 190180 | GEN-XR  | Human mRNA for transforming growth factor-beta (TGF-beta)                          | 1632 | 791C>T   | T264I |
| X02812 | X02812 | 190180 | GEN-XR  | Human mRNA for transforming growth factor-beta (TGF-beta)                          | 1807 | 966C>T   | S     |
| X02812 | X02812 | 190180 | GEN-XR  | Human mRNA for transforming growth factor-beta (TGF-beta)                          | 1930 | 1089G>A  | S     |
| X02812 | X02812 | 190180 | GEN-XR  | Human mRNA for transforming growth factor-beta (TGF-beta)                          | 1942 | 1101C>T  | S     |
| X02812 | X02812 | 190180 | GEN-XR  | Human mRNA for transforming growth factor-beta (TGF-beta)                          | 2013 | 1172G>A  | S391N |

|        |        |        |        |                                                                                  |      |                     |       |
|--------|--------|--------|--------|----------------------------------------------------------------------------------|------|---------------------|-------|
| X03172 | X03172 | 192340 | GEN-ZM | transforming growth factor-<br>beta (TGF-beta)                                   | 379  | 356T>G              | V119G |
| X03635 | X03635 | 133430 | GEN-50 | Human mRNA for<br>vasopressin precursor                                          | 390  | 30T>C               | S     |
| X03635 | X03635 | 133430 | GEN-50 | estrogen receptors                                                               | 390  | 30T>C               | S     |
| X03635 | X03635 | 133430 | GEN-50 | estrogen receptors                                                               | 424  | 64G>C               | E22Q  |
| X03635 | X03635 | 133430 | GEN-50 | estrogen receptors                                                               | 617  | 257C>T              | A86V  |
| X03635 | X03635 | 133430 | GEN-50 | estrogen receptors                                                               | 621  | 261G>C              | S     |
| X03635 | X03635 | 133430 | GEN-50 | estrogen receptors                                                               | 829  | 469C>T              | F     |
| X03635 | X03635 | 133430 | GEN-50 | estrogen receptors                                                               | 1335 | 975C>G              | S     |
| X03635 | X03635 | 133430 | GEN-50 | estrogen receptors                                                               | 1335 | 975C>G              | S     |
| X03635 | X03635 | 133430 | GEN-50 | estrogen receptors                                                               | 1451 | 1091T>A             | V364E |
| X03635 | X03635 | 133430 | GEN-50 | estrogen receptors                                                               | 1674 | 1314G>A             | M438I |
| X03635 | X03635 | 133430 | GEN-50 | estrogen receptors                                                               | 2142 | 1782A>G             | S     |
| X03635 | X03635 | 133430 | GEN-50 | estrogen receptors                                                               | 2354 | 1994A>G             | 3     |
| X03635 | X03635 | 133430 | GEN-50 | estrogen receptors                                                               | 2550 | 2190A>C             | 3     |
| X03635 | X03635 | 133430 | GEN-50 | estrogen receptors                                                               | 2733 | 2373C>G             | 3     |
| X03635 | X03635 | 133430 | GEN-50 | estrogen receptors                                                               | 3181 | 2821T>C             | 3     |
| X03635 | X03635 | 133430 | GEN-50 | estrogen receptors                                                               | 3338 | 2978C>T             | 3     |
| X03635 | X03635 | 133430 | GEN-50 | estrogen receptors                                                               | 3652 | 3292-<br>3294CCT>CC | 3     |
| X03635 | X03635 | 133430 | GEN-50 | estrogen receptors                                                               | 3652 | 3292-<br>3294delCCT | 3     |
| X03635 | X03635 | 133430 | GEN-50 | estrogen receptors                                                               | 3896 | 3536C>A             | 3     |
| X03635 | X03635 | 133430 | GEN-50 | estrogen receptors                                                               | 4378 | 4018T>C             | 3     |
| X03635 | X03635 | 133430 | GEN-50 | estrogen receptors                                                               | 6287 | 5927T>C             | 3     |
| X04409 | X04409 | 139320 | GEN-7Q | Guanine nucleotide binding<br>protein (G protein), alpha<br>stimulating activity | 363  | 351C>T              | S     |
| X04409 | X04409 | 139320 | GEN-7Q | polypeptide 1                                                                    | 525  | 513C>T              | S     |
| X04409 | X04409 | 139320 | GEN-7Q | Guanine nucleotide binding<br>protein (G protein), alpha<br>stimulating activity | 967  | 955C>A              | R319S |

|        |        |        |         |                                                                                                                            |      |         |       |
|--------|--------|--------|---------|----------------------------------------------------------------------------------------------------------------------------|------|---------|-------|
| X04409 | X04409 | 139320 | GEN-7Q  | stimulating activity<br>polypeptide 1<br>Guanine nucleotide binding<br>protein (G protein), alpha<br>stimulating activity  | 1023 | 1011C>A | S     |
| X04409 | X04409 | 139320 | GEN-7Q  | stimulating activity<br>polypeptide 1<br>Guanine nucleotide binding<br>protein (G protein), alpha<br>stimulating activity  | 1083 | 1071C>T | S     |
| X04409 | X04409 | 139320 | GEN-7Q  | stimulating activity<br>polypeptide 1<br>Guanine nucleotide binding<br>protein (G protein), alpha<br>stimulating activity  | 1213 | 1201T>G | 3     |
| X04409 | X04409 | 139320 | GEN-7Q  | stimulating activity<br>polypeptide 1<br>Guanine nucleotide binding<br>protein (G protein), alpha<br>stimulating activity  | 1450 | 1438A>C | 3     |
| X04707 | X04707 | 190160 | GEN-CCA | stimulating activity<br>polypeptide 1<br>Human c-erb-A mRNA for<br>thyroid hormone receptor                                | 1295 | 995T>C  | I332T |
| X05199 | X05199 | 173350 | GEN-PU  | stimulating activity<br>polypeptide 1<br>Human mRNA for<br>plasminogen                                                     | 384  | 330C>T  | S     |
| X05199 | X05199 | 173350 | GEN-PU  | stimulating activity<br>polypeptide 1<br>Human mRNA for<br>plasminogen                                                     | 825  | 771C>T  | S     |
| X05199 | X05199 | 173350 | GEN-PU  | stimulating activity<br>polypeptide 1<br>Human mRNA for<br>plasminogen                                                     | 996  | 942C>T  | S     |
| X05199 | X05199 | 173350 | GEN-PU  | stimulating activity<br>polypeptide 1<br>Human mRNA for<br>plasminogen                                                     | 1137 | 1083A>G | S     |
| X05199 | X05199 | 173350 | GEN-PU  | stimulating activity<br>polypeptide 1<br>Human mRNA for<br>plasminogen                                                     | 1485 | 1431C>T | S     |
| X05199 | X05199 | 173350 | GEN-PU  | stimulating activity<br>polypeptide 1<br>Human mRNA for<br>plasminogen                                                     | 2340 | 2286T>G | S     |
| X05199 | X05199 | 173350 | GEN-PU  | stimulating activity<br>polypeptide 1<br>Human mRNA for<br>plasminogen                                                     | 2532 | 2478G>A | 3     |
| X05199 | X05199 | 173350 | GEN-PU  | stimulating activity<br>polypeptide 1<br>Human mRNA for<br>plasminogen                                                     | 2606 | 2552T>G | 3     |
| X05344 | X05344 | 116840 | GEN-PW  | stimulating activity<br>polypeptide 1<br>Human mRNA for<br>cathepsin D from<br>oestrogen responsive<br>breast cancer cells | 1583 | 1581C>G | 3     |
| X05344 | X05344 | 116840 | GEN-PW  | stimulating activity<br>polypeptide 1<br>Human mRNA for<br>cathepsin D from<br>breast cancer cells                         | 1703 | 1701C>T | 3     |



|        |        |        |         |                                                                                   |      |          |        |
|--------|--------|--------|---------|-----------------------------------------------------------------------------------|------|----------|--------|
| X05344 | X05344 | 116840 | GEN-PW  | cathepsin D from<br>oestrogen responsive<br>breast cancer cells                   | 1754 | 1752G>A  | 3      |
| X05344 | X05344 | 116840 | GEN-PW  | Human mRNA for<br>cathepsin D from<br>oestrogen responsive<br>breast cancer cells | 1798 | 1796A>C  | 3      |
| X05344 | X05344 | 116840 | GEN-PW  | Human mRNA for<br>cathepsin D from<br>oestrogen responsive<br>breast cancer cells | 1837 | 1835A>C  | 3      |
| X05344 | X05344 | 116840 | GEN-PW  | Human mRNA for<br>cathepsin D from<br>oestrogen responsive<br>breast cancer cells | 1901 | 1899C>T  | 3      |
| X05344 | X05344 | 116840 | GEN-PW  | Human mRNA for<br>cathepsin D from<br>oestrogen responsive<br>breast cancer cells | 1975 | 1973T>G  | 3      |
| X05615 | X05615 | 188450 | GEN-188 | Human mRNA for<br>thyroglobulin                                                   | 5945 | 5904G>A  | S      |
| X05615 | X05615 | 188450 | GEN-188 | Human mRNA for<br>thyroglobulin                                                   | 7627 | 7586G>A  | R2529Q |
| X05615 | X05615 | 188450 | GEN-188 | Human mRNA for<br>thyroglobulin                                                   | 7704 | 7663G>T  | V2555F |
| X05615 | X05615 | 188450 | GEN-188 | Human mRNA for<br>thyroglobulin                                                   | 7958 | 7917C>T  | S      |
| X06318 | X06318 | 176970 | GEN-KY  | Protein kinase C, beta 1                                                          | 83   | (-54)G>C | 5      |
| X06318 | X06318 | 176970 | GEN-KY  | Protein kinase C, beta 1                                                          | 940  | 804G>A   | S      |
| X06318 | X06318 | 176970 | GEN-KY  | Protein kinase C, beta 1                                                          | 1327 | 1191T>C  | S      |
| X06318 | X06318 | 176970 | GEN-KY  | Protein kinase C, beta 1                                                          | 1906 | 1770C>T  | S      |
| X06562 | X06562 | 600946 | GEN-6D  | Growth hormone receptor                                                           | 3392 | 3349A>T  | 3      |
| X06562 | X06562 | 600946 | GEN-6D  | Growth hormone receptor                                                           | 4145 | 4102G>A  | 3      |
| X07549 | X07549 | 116820 | GEN-1DZ | Human mRNA for<br>cathepsin H                                                     | 276  | 244T>C   | 3      |

(E.C.3.4.22.16.)

|        |        |        |         |                                                             |      |                                |       |
|--------|--------|--------|---------|-------------------------------------------------------------|------|--------------------------------|-------|
| X07549 | X07549 | 116820 | GEN-1DZ | Human mRNA for cathepsin H (E.C.3.4.22.16.)                 | 664  | 632G>A                         | 3     |
| X07549 | X07549 | 116820 | GEN-1DZ | Human mRNA for cathepsin H (E.C.3.4.22.16.)                 | 1006 | 974G>A                         | 3     |
| X07549 | X07549 | 116820 | GEN-1DZ | Human mRNA for cathepsin H (E.C.3.4.22.16.)                 | 1029 | 997G>A                         | 3     |
| X13589 | X13589 | 107910 | GEN-56  | Cytochrome P450, subfamily XIX (aromatization of androgens) | 364  | 240A>G                         | S     |
| X13589 | X13589 | 107910 | GEN-56  | Cytochrome P450, subfamily XIX (aromatization of androgens) | 914  | 790C>T                         | R264C |
| X13589 | X13589 | 107910 | GEN-56  | Cytochrome P450, subfamily XIX (aromatization of androgens) | 914  | 790C>T                         | R264C |
| X13589 | X13589 | 107910 | GEN-56  | Cytochrome P450, subfamily XIX (aromatization of androgens) | 1655 | 1531C>T                        | 3     |
| X13589 | X13589 | 107910 | GEN-56  | Cytochrome P450, subfamily XIX (aromatization of androgens) | 1796 | 1672G>T                        | 3     |
| X13629 | X13629 | 107690 | GEN-100 | Human intestinal mRNA for apolipoprotein A-IV               | 881  | 836G>A                         | R279K |
| X13629 | X13629 | 107690 | GEN-100 | Human intestinal mRNA for apolipoprotein A-IV               | 1185 | 1140G>T                        | Q380H |
| X13629 | X13629 | 107690 | GEN-100 | Human intestinal mRNA for apolipoprotein A-IV               | 1302 | 1257 <sup>1</sup> 1258ins CTGT | F     |
| X13916 | X13916 | 107770 | GEN-1Q1 | Human mRNA for LDL-receptor related protein                 | 1636 | 1170T>C                        | S     |
| X13916 | X13916 | 107770 | GEN-1Q1 | Human mRNA for LDL-receptor related protein                 | 1675 | 1209C>T                        | S     |
| X13916 | X13916 | 107770 | GEN-1Q1 | Human mRNA for LDL-receptor related protein                 | 2805 | 2339C>T                        | T780I |

|        |        |        |         |                                                              |      |                      |        |
|--------|--------|--------|---------|--------------------------------------------------------------|------|----------------------|--------|
| X13916 | X13916 | 107770 | GEN-1Q1 | Human mRNA for LDL-receptor related protein                  | 3853 | 3387T>C              | S      |
| X13916 | X13916 | 107770 | GEN-1Q1 | Human mRNA for LDL-receptor related protein                  | 6443 | 5977C>T              | R1993W |
| X13916 | X13916 | 107770 | GEN-1Q1 | Human mRNA for LDL-receptor related protein                  | 7036 | 6570C>T              | S      |
| X13916 | X13916 | 107770 | GEN-1Q1 | Human mRNA for LDL-receptor related protein                  | 8608 | 8142G>A              | S      |
| X13916 | X13916 | 107770 | GEN-1Q1 | Human mRNA for LDL-receptor related protein                  | 8923 | 8457C>T              | S      |
| X13916 | X13916 | 107770 | GEN-1Q1 | Human mRNA for LDL-receptor related protein                  | 9034 | 8568G>T              | S      |
| X13916 | X13916 | 107770 | GEN-1Q1 | Human mRNA for LDL-receptor related protein                  | 9040 | 8574C>T              | S      |
| X13916 | X13916 | 107770 | GEN-1Q1 | Human mRNA for LDL-receptor related protein                  | 9391 | 8925T>C              | S      |
| X15357 | X15357 | 108960 | GEN-KUV | Human mRNA for natriuretic peptide receptor (ANP-A receptor) | 1066 | 1023G>C              | M341I  |
| X15357 | X15357 | 108960 | GEN-KUV | Human mRNA for natriuretic peptide receptor (ANP-A receptor) | 1657 | 1614C>T              | S      |
| X15357 | X15357 | 108960 | GEN-KUV | Human mRNA for natriuretic peptide receptor (ANP-A receptor) | 2859 | 2816G>A              | R939Q  |
| X15357 | X15357 | 108960 | GEN-KUV | Human mRNA for natriuretic peptide receptor (ANP-A receptor) | 2983 | 2940G>A              | S      |
| X15357 | X15357 | 108960 | GEN-KUV | Human mRNA for natriuretic peptide receptor (ANP-A receptor) | 3259 | 3216delC             | F      |
| X15357 | X15357 | 108960 | GEN-KUV | Human mRNA for natriuretic peptide receptor (ANP-A receptor) | 3589 | 3546*3547ins<br>GAAA | F      |
| X51362 | X51362 | 126450 | GEN-31W | Dopamine Receptor D2                                         | 588  | 423G>A               | S      |
| X51362 | X51362 | 126450 | GEN-31W | Dopamine Receptor D2                                         | 1104 | 939C>T               | S      |
| X51362 | X51362 | 126450 | GEN-31W | Dopamine Receptor D2                                         | 1122 | 957T>C               | S      |
| X51362 | X51362 | 126450 | GEN-31W | Dopamine Receptor D2                                         | 1248 | 1083A>G              | S      |

|        |        |        |                |                                                              |      |         |       |
|--------|--------|--------|----------------|--------------------------------------------------------------|------|---------|-------|
| X51362 | X51362 | 126450 | 31W<br>GEN-31W | Dopamine Receptor D2                                         | 1488 | 1323T>C | S     |
| X51362 | X51362 | 126450 | 31W<br>GEN-31W | Dopamine Receptor D2                                         | 1548 | 1383A>G | 3     |
| X51362 | X51362 | 126450 | 31W<br>GEN-31W | Dopamine Receptor D2                                         | 2361 | 2196C>T | 3     |
| X51416 | X51416 | 601998 | GEN-57         | STERIOD HORMONE<br>RECEPTOR ERR1                             | 2285 | 2222G>A | 3     |
| X52773 | X52773 | 180245 | GEN-74         | Retinoid X receptor, alpha                                   | 1744 | 1669G>A | 3     |
| X55005 | X55005 | 190120 | GEN-35S        | Human c-erbA-1 mRNA for<br>thyroid hormone receptor<br>alpha | 493  | 27A>G   | S     |
| X55005 | X55005 | 190120 | GEN-35S        | Human c-erbA-1 mRNA for<br>thyroid hormone receptor<br>alpha | 1523 | 1057G>A | V353I |
| X59498 | X59498 | 176300 | GEN-RU         | H.sapiens ttr mRNA for<br>transthyretin                      | 92   | 71G>A   | G24D  |
| X59498 | X59498 | 176300 | GEN-RU         | H.sapiens ttr mRNA for<br>transthyretin                      | 177  | 156G>T  | S     |
| X59498 | X59498 | 176300 | GEN-RU         | H.sapiens ttr mRNA for<br>transthyretin                      | 380  | 359C>T  | S120F |
| X59842 | X59842 | 600214 | GEN-3A3        | Human PBX2 mRNA                                              | 2339 | 2043T>G | 3     |
| X63359 | X63359 | 600070 | GEN-3DC        | H.sapiens UGT2B10<br>mRNA for udp<br>glucuronosyltransferase | 1516 | 1506C>T | S     |
| X63359 | X63359 | 600070 | GEN-3DC        | H.sapiens UGT2B10<br>mRNA for udp<br>glucuronosyltransferase | 2714 | 2704G>A | 3     |
| X63522 | X63522 | 180246 | GEN-75         | MHC class I promoter<br>binding protein                      | 1331 | 1152T>C | S     |
| X68596 | X68596 | 168468 | GEN-3IJ        | H.sapiens mRNA for<br>parathyroid hormone<br>receptor        | 1563 | 1389T>C | S     |
| X69141 | X69141 | 184420 | GEN-3J9        | H.sapiens mRNA for<br>squalene synthase                      | 112  | 21T>C   | S     |
| X69141 | X69141 | 184420 | GEN-3J9        | H.sapiens mRNA for<br>squalene synthase                      | 292  | 201C>T  | S     |
| X69141 | X69141 | 184420 | GEN-3J9        | H.sapiens mRNA for<br>squalene synthase                      | 1436 | 1345T>C | 3     |

|        |        |        |         |                                                                                                                                    |      |          |       |
|--------|--------|--------|---------|------------------------------------------------------------------------------------------------------------------------------------|------|----------|-------|
| X69141 | X69141 | 184420 | GEN-3J9 | H.sapiens mRNA for squalene synthase                                                                                               | 1579 | 1488T>C  | 3     |
| X69141 | X69141 | 184420 | GEN-3J9 | H.sapiens mRNA for squalene synthase                                                                                               | 1621 | 1530C>T  | 3     |
| X69141 | X69141 | 184420 | GEN-3J9 | H.sapiens mRNA for squalene synthase                                                                                               | 1719 | 1628A>C  | 3     |
| X69141 | X69141 | 184420 | GEN-3J9 | H.sapiens mRNA for squalene synthase                                                                                               | 1904 | 1813G>C  | 3     |
| X69699 | X69699 | 167415 | GEN-3JS | H.sapiens Pax8 mRNA                                                                                                                | 1412 | 1413G>C  | 3     |
| X69699 | X69699 | 167415 | GEN-3JS | H.sapiens Pax8 mRNA                                                                                                                | 2164 | 2165T>G  | 3     |
| X69699 | X69699 | 167415 | GEN-3JS | H.sapiens Pax8 mRNA                                                                                                                | 2508 | 2509T>C  | 3     |
| X69699 | X69699 | 167415 | GEN-3JS | H.sapiens Pax8 mRNA                                                                                                                | 2514 | 2515A>C  | 3     |
| X69699 | X69699 | 167415 | GEN-3JS | H.sapiens Pax8 mRNA                                                                                                                | 2552 | 2553A>C  | 3     |
| X70811 | X70811 | 109691 | GEN-3KK | beta-3-adrenergic receptor                                                                                                         | 315  | 190T>C   | W64R  |
| X70811 | X70811 | 109691 | GEN-3KK | beta-3-adrenergic receptor                                                                                                         | 315  | 190T>C   | W64R  |
| X71440 | X71440 | None   | GEN-3KS | H.sapiens mRNA for peroxisomal acyl-CoA oxidase                                                                                    | 949  | 936G>C   | M312I |
| X75958 | X75958 | 600456 | GEN-3OE | H.sapiens trkB mRNA for protein-tyrosine kinase                                                                                    | 30   | (-68)C>G | 5     |
| X75958 | X75958 | 600456 | GEN-3OE | H.sapiens trkB mRNA for protein-tyrosine kinase                                                                                    | 2010 | 1913A>G  | 3     |
| X75958 | X75958 | 600456 | GEN-3OE | H.sapiens trkB mRNA for protein-tyrosine kinase                                                                                    | 2101 | 2004C>T  | 3     |
| X76180 | X76180 | 600228 | GEN-N5  | Solute carrier family 9 (sodium/hydrogen exchanger), isoform 1 (antiporter, Na <sup>+</sup> /H <sup>+</sup> , amiloride sensitive) | 1901 | 1802G>A  | G601D |
| X77383 | X77383 | 600550 | GEN-3PT | H.sapiens mRNA for cathepsin-O                                                                                                     | 1595 | 1546C>T  | 3     |
| X77533 | X77533 | 602730 | GEN-3Q3 | H.sapiens mRNA for activin type II receptor                                                                                        | 1462 | 1458C>T  | S     |
| X78873 | X78873 | 601792 | GEN-    | H.sapiens mRNA for                                                                                                                 | 538  | 535G>A   | D179N |

|        |        |        |                    |                                                                                                               |      |         |        |
|--------|--------|--------|--------------------|---------------------------------------------------------------------------------------------------------------|------|---------|--------|
| X78873 | X78873 | 601792 | 3RQ<br>GEN-        | inhibitor 2 gene                                                                                              | 812  | 809G>A  | 3      |
| X79483 | X79483 | 602399 | 3RQ<br>GEN-<br>LPR | H.sapiens mRNA for<br>inhibitor 2 gene<br>H.sapiens ERK6 mRNA for<br>extracellular signal<br>regulated kinase | 1287 | 1254T>G | 3      |
| X79537 | X79537 | 603942 | GEN-<br>3TA        | H.sapiens mRNA for<br>glycogenin                                                                              | 635  | 552G>A  | S      |
| X79537 | X79537 | 603942 | GEN-<br>3TA        | H.sapiens mRNA for<br>glycogenin                                                                              | 1381 | 1298A>G | 3      |
| X83368 | X83368 | 601232 | GEN-<br>3XT        | H.sapiens mRNA for<br>phosphatidylinositol 3<br>kinase gamma                                                  | 3884 | 3561C>T | 3      |
| X87212 | X87212 | 602365 | GEN-<br>42U        | H.sapiens mRNA for<br>cathepsin C                                                                             | 318  | 285G>T  | S      |
| X87212 | X87212 | 602365 | GEN-<br>42U        | H.sapiens mRNA for<br>cathepsin C                                                                             | 870  | 837G>C  | Q279H  |
| X87212 | X87212 | 602365 | GEN-<br>42U        | H.sapiens mRNA for<br>cathepsin C                                                                             | 1390 | 1357A>G | I453V  |
| X87212 | X87212 | 602365 | GEN-<br>42U        | H.sapiens mRNA for<br>cathepsin C                                                                             | 1758 | 1725A>C | 3      |
| X92521 | X92521 | 601807 | GEN-480            | H.sapiens mRNA for MMP-<br>19 protein                                                                         | 1722 | 1621T>G | 3      |
| X92720 | X92720 | 261650 | GEN-484            | H.sapiens mRNA for<br>phosphoenolpyruvate<br>carboxykinase                                                    | 1494 | 1428A>C | R476S  |
| X95190 | X95190 | 601641 | GEN-<br>49Y        | H.sapiens mRNA for<br>Branched chain Acyl-CoA<br>Oxidase                                                      | 1394 | 1302C>T | S      |
| X95190 | X95190 | 601641 | GEN-<br>49Y        | H.sapiens mRNA for<br>Branched chain Acyl-CoA<br>Oxidase                                                      | 1934 | 1842C>A | S      |
| Y00285 | Y00285 | 147280 | GEN-6I             | IGF-2 receptor                                                                                                | 4613 | 4466G>A | S1489N |
| Y00285 | Y00285 | 147280 | GEN-6I             | IGF-2 receptor                                                                                                | 6371 | 6224C>T | T2075M |
| Y00285 | Y00285 | 147280 | GEN-6I             | IGF-2 receptor                                                                                                | 6813 | 6666C>T | S      |
| Y00285 | Y00285 | 147280 | GEN-6I             | IGF-2 receptor                                                                                                | 7150 | 7003G>A | V2335M |
| Y00285 | Y00285 | 147280 | GEN-6I             | IGF-2 receptor                                                                                                | 8685 | 8538C>A | 3      |
| Y00406 | Y00406 | 274500 | GEN-6J             | Peroxidase (thyroid)                                                                                          | 2185 | 2145T>C | S      |
| Y00406 | Y00406 | 274500 | GEN-6J             | Peroxidase (thyroid)                                                                                          | 2213 | 2173C>A | P725T  |
| Y00406 | Y00406 | 274500 | GEN-6J             | Peroxidase (thyroid)                                                                                          | 2580 | 2540C>T | A847V  |

|        |        |        |         |                                                                |      |         |        |
|--------|--------|--------|---------|----------------------------------------------------------------|------|---------|--------|
| Y00406 | Y00406 | 274500 | GEN-6J  | Peroxidase (thyroid)                                           | 2923 | 2883C>G | 3      |
| Y00749 | Y00749 | 131240 | GEN-P7  | Endothelin 1                                                   | 846  | 594G>T  | K198N  |
| Y08110 | Y08110 | 602005 | GEN-1FK | H.sapiens mRNA for mosaic protein LR11                         | 3641 | 3561T>G | S      |
| Y08110 | Y08110 | 602005 | GEN-1FK | H.sapiens mRNA for mosaic protein LR11                         | 3818 | 3738C>T | S      |
| Y08110 | Y08110 | 602005 | GEN-1FK | H.sapiens mRNA for mosaic protein LR11                         | 5158 | 5078G>A | S1693N |
| Y08110 | Y08110 | 602005 | GEN-1FK | H.sapiens mRNA for mosaic protein LR11                         | 6571 | 6491G>A | R2164K |
| Y10055 | Y10055 | 602839 | GEN-1IC | H.sapiens mRNA for phosphoinositide 3-kinase                   | 954  | 758G>A  | S253N  |
| Y10055 | Y10055 | 602839 | GEN-1IC | H.sapiens mRNA for phosphoinositide 3-kinase                   | 2491 | 2295C>T | S      |
| Y10055 | Y10055 | 602839 | GEN-1IC | H.sapiens mRNA for phosphoinositide 3-kinase                   | 3004 | 2808C>T | S      |
| Y11525 | Y11525 | 116897 | GEN-1KR | H.sapiens mRNA for CCAAT/enhancer binding protein alpha        | 922  | 773C>T  | A258V  |
| Y11525 | Y11525 | 116897 | GEN-1KR | H.sapiens mRNA for CCAAT/enhancer binding protein alpha        | 1007 | 858G>A  | S      |
| Y11525 | Y11525 | 116897 | GEN-1KR | H.sapiens mRNA for CCAAT/enhancer binding protein alpha        | 1441 | 1292G>A | 3      |
| Y11525 | Y11525 | 116897 | GEN-1KR | H.sapiens mRNA for CCAAT/enhancer binding protein alpha        | 2327 | 2178T>C | 3      |
| Y15409 | Y15409 | 602671 | GEN-1U1 | Homo sapiens mRNA for putative glucose 6-phosphate translocase | 1393 | 1224G>A | S      |
| Y15409 | Y15409 | 602671 | GEN-1U1 | Homo sapiens mRNA for putative glucose 6-phosphate translocase | 1584 | 1415C>G | 3      |
| Y15409 | Y15409 | 602671 | GEN-1U1 | Homo sapiens mRNA for putative glucose 6-phosphate translocase | 1877 | 1708C>T | 3      |
| Y15521 | Y15521 | None   | GEN-MEN | phosphate translocase                                          | 1622 | 1622A>G | K541R  |
| Z11695 | Z11695 | 176948 | GEN-1L1 | H.sapiens 40 kDa protein kinase related to rat ERK2            | 1287 | 1153G>A | 3      |

|        |        |        |         |                                                    |      |         |       |
|--------|--------|--------|---------|----------------------------------------------------|------|---------|-------|
| Z11696 | Z11696 | 601795 | GEN-1L0 | H.sapiens 44kDa protein kinase related to rat ERK1 | 449  | 449T>G  | 1150S |
| Z82022 | Z82022 | 191350 | GEN-3WH | H.sapiens mRNA for GlcNac-1-P transferase          | 1256 | 1153A>G | 1385V |
| Z82022 | Z82022 | 191350 | GEN-3WH | H.sapiens mRNA for GlcNac-1-P transferase          | 1491 | 1388G>A | 3     |
| Z82022 | Z82022 | 191350 | GEN-3WH | H.sapiens mRNA for GlcNac-1-P transferase          | 1723 | 1620T>C | 3     |

Table 17.  
Identified  
Variances  
In Genes  
for  
Pathways  
Identified  
in  
Endocrine  
and  
Metabolic  
Disease  
and  
Related  
Disorders

|         |         |        |         |                                                               |       |          |       |
|---------|---------|--------|---------|---------------------------------------------------------------|-------|----------|-------|
| AB00026 | AB00026 | 602784 | GEN-16N | Human mRNA for prepro cortistatin like peptide, complete cds  | 215   | 210T>C   | S     |
| AB00102 | AB00102 | 180903 | GEN-18S | Homo sapiens mRNA for brain ryanodine receptor, complete cds  | 14689 | 14603T>G | 3     |
| AB00102 | AB00102 | 180903 | GEN-18S | Homo sapiens mRNA for brain ryanodine receptor, complete cds  | 15521 | 15435G>A | 3     |
| AB00132 | AB00132 | 600170 | GEN-KYP | Human AQP3 gene for aquaporine 3 (water channel), partial cds | 1203  | 1143G>A  | 3     |
| AB00528 | AB00528 | 300135 | GEN-KVU | Homo sapiens mRNA for ABC transporter 7 protein, complete cds | 2137  | 2069A>T  | H690L |
| AB00529 | AB00529 | 170290 | GEN-W4  | Homo sapiens mRNA for                                         | 2197  | 2073A>T  | 3     |



|          |   |          |        |         |                                                                       |      |         |       |
|----------|---|----------|--------|---------|-----------------------------------------------------------------------|------|---------|-------|
| AB00942  | 3 | AB00942  | 600130 | GEN-MDN | perilipin, complete cds                                               | 1016 | 534C>T  | S     |
| AB01071  | 6 | AB01071  | 602601 | GEN-1SQ | Homo sapiens gene for apobec-1                                        | 1071 | 1010T>A | 3     |
| AB01071  | 0 | AB01071  | 602601 | GEN-1SQ | Homo sapiens mRNA for lectin-like oxidized LDL receptor, complete cds | 1073 | 1012T>C | 3     |
| AB01071  | 0 | AB01071  | 602601 | GEN-1SQ | Homo sapiens mRNA for lectin-like oxidized LDL receptor, complete cds | 1073 | 1012T>C | 3     |
| AB01071  | 0 | AB01071  | 602601 | GEN-1SQ | Homo sapiens mRNA for lectin-like oxidized LDL receptor, complete cds | 1801 | 1740A>G | 3     |
| AB01071  | 0 | AB01071  | 602601 | GEN-1SQ | Homo sapiens mRNA for lectin-like oxidized LDL receptor, complete cds | 2199 | 2138G>A | 3     |
| AB02068  | 0 | AB02068  | None   | GEN-LAX | Homo sapiens complete cds KIAA0873 protein, partial cds               | 3854 | 3854A>G | 3     |
| AF000234 | 3 | AF000234 | 600846 | GEN-16J | PURINERGIC RECEPTOR P2X, LIGAND-GATED ION CHANNEL, 4; P2RX4           | 365  | 365C>T  | P122L |
| AF000234 | 6 | AF000234 | 600846 | GEN-16J | PURINERGIC RECEPTOR P2X, LIGAND-GATED ION CHANNEL, 4; P2RX4           | 381  | 381G>A  | S     |
| AF000234 | 0 | AF000234 | 600846 | GEN-16J | PURINERGIC RECEPTOR P2X, LIGAND-GATED ION CHANNEL, 4; P2RX4           | 624  | 624A>G  | S     |
| AF000234 | 0 | AF000234 | 600846 | GEN-16J | PURINERGIC RECEPTOR P2X, LIGAND-GATED ION CHANNEL, 4; P2RX4           | 641  | 641C>T  | P214L |
| AF000234 | 0 | AF000234 | 600846 | GEN-16J | PURINERGIC RECEPTOR P2X, LIGAND-GATED ION CHANNEL, 4; P2RX4           | 1161 | 1161T>C | 3     |
| AF000571 | 0 | AF000571 | 192500 | GEN-15U | K+ channel (KvLQT1)                                                   | 545  | 435C>T  | S     |
| AF000571 | 0 | AF000571 | 192500 | GEN-15U | K+ channel (KvLQT1)                                                   | 1748 | 1638G>A | S     |
| AF000571 | 0 | AF000571 | 192500 | GEN-15U | K+ channel (KvLQT1)                                                   | 2360 | 2250G>A | 3     |

|          |          |        |             |                                                                                             |      |         |       |
|----------|----------|--------|-------------|---------------------------------------------------------------------------------------------|------|---------|-------|
| AF000571 | AF000571 | 192500 | 15U<br>GEN- | K+ channel (KvLQT1)                                                                         | 2552 | 2442C>T | 3     |
| AF000571 | AF000571 | 192500 | 15U<br>GEN- | K+ channel (KvLQT1)                                                                         | 3016 | 2906A>G | 3     |
| AF000571 | AF000571 | 192500 | 15U<br>GEN- | K+ channel (KvLQT1)                                                                         | 3073 | 2963A>G | 3     |
| AF001174 | AF001174 | 602898 | 15U<br>GEN- | Homo sapiens p38beta2<br>MAP kinase mRNA,<br>complete cds                                   | 1044 | 1038T>C | S     |
| AF004709 | AF004709 | 602899 | GEN-UX      | Homo sapiens stress-<br>activated protein kinase 4<br>mRNA, complete cds                    | 432  | 384G>A  | S     |
| AF005043 | AF005043 | 603501 | GEN-VX      | Homo sapiens poly(ADP-<br>ribose) glycohydrolase<br>(hPARG) mRNA, complete<br>cds           | 1916 | 1750G>A | A584T |
| AF005043 | AF005043 | 603501 | GEN-VX      | Homo sapiens poly(ADP-<br>ribose) glycohydrolase<br>(hPARG) mRNA, complete<br>cds           | 3780 | 3614C>G | 3     |
| AF009620 | AF009620 | 601763 | GEN-<br>1HV | Homo sapiens apoptotic<br>caspase Mch5-beta<br>mRNA, alternatively<br>spliced, complete cds | 808  | 808C>G  | H270D |
| AF009620 | AF009620 | 601763 | GEN-<br>1HV | Homo sapiens apoptotic<br>caspase Mch5-beta<br>mRNA, alternatively<br>spliced, complete cds | 915  | 915G>A  | S     |
| AF016709 | AF016709 | 602836 | GEN-<br>1NE | PURINERGIC RECEPTOR<br>P2X, LIGAND-GATED ION<br>CHANNEL, 5; P2RX5                           | 1023 | 987T>C  | S     |
| AF016709 | AF016709 | 602836 | GEN-<br>1NE | PURINERGIC RECEPTOR<br>P2X, LIGAND-GATED ION<br>CHANNEL, 5; P2RX5                           | 1025 | 989T>C  | F330S |
| AF016709 | AF016709 | 602836 | GEN-<br>1NE | PURINERGIC RECEPTOR<br>P2X, LIGAND-GATED ION<br>CHANNEL, 5; P2RX5                           | 1090 | 1054G>C | E352Q |
| AF016709 | AF016709 | 602836 | GEN-<br>1NE | PURINERGIC RECEPTOR<br>P2X, LIGAND-GATED ION<br>CHANNEL, 5; P2RX5                           | 1321 | 1285G>A | 3     |

|          |          |        |         |                                                                            |      |         |       |
|----------|----------|--------|---------|----------------------------------------------------------------------------|------|---------|-------|
| AF016709 | AF016709 | 602836 | GEN-1NE | PURINERGIC RECEPTOR P2X, LIGAND-GATED ION CHANNEL, 5; P2RX5                | 1424 | 1388C>G | 3     |
| AF016709 | AF016709 | 602836 | GEN-1NE | PURINERGIC RECEPTOR P2X, LIGAND-GATED ION CHANNEL, 5; P2RX5                | 1512 | 1476G>A | 3     |
| AF016709 | AF016709 | 602836 | GEN-1NE | PURINERGIC RECEPTOR P2X, LIGAND-GATED ION CHANNEL, 5; P2RX5                | 1743 | 1707A>G | 3     |
| AF016709 | AF016709 | 602836 | GEN-1NE | PURINERGIC RECEPTOR P2X, LIGAND-GATED ION CHANNEL, 5; P2RX5                | 1858 | 1822A>G | 3     |
| AF021792 | AF021792 | 603167 | GEN-2A5 | Homo sapiens Bcl-X/Bcl-2 binding protein (BAD) mRNA, partial cds           | 781  | 781G>A  | 3     |
| AF021792 | AF021792 | 603167 | GEN-2A5 | Homo sapiens Bcl-X/Bcl-2 binding protein (BAD) mRNA, partial cds           | 883  | 883C>A  | 3     |
| HRH1     | AF026261 | 600167 | GEN-26W | Histamine receptor H1 mRNA, partial cds                                    | 1068 | 1068A>G | S     |
| AVPR1B   | AF030512 | 600264 | GEN-4FF | Homo sapiens small cell vasopressin subtype 1b receptor mRNA, complete cds | 273  | 150G>A  | S     |
| AF030625 | AF030625 | 600821 | GEN-2   | Vasopressin V1A receptor                                                   | 314  | 291C>T  | S     |
| AF030625 | AF030625 | 600821 | GEN-2   | Vasopressin V1A receptor                                                   | 431  | 408T>C  | S     |
| AF030625 | AF030625 | 600821 | GEN-2   | Vasopressin V1A receptor                                                   | 506  | 483A>G  | S     |
| ITGA7    | AF032108 | 600536 | GEN-2NO | Homo sapiens integrin alpha-7 mRNA, complete cds                           | 527  | 366G>A  | S     |
| AF033850 | AF033850 | 602384 | GEN-2OB | Homo sapiens phospholipase D2 (PLD2) mRNA, complete cds                    | 795  | 634C>T  | R212C |
| AF033850 | AF033850 | 602384 | GEN-2OB | Homo sapiens phospholipase D2 (PLD2) mRNA, complete cds                    | 2531 | 2370G>A | S     |
| AF033850 | AF033850 | 602384 | GEN-2OB | Homo sapiens phospholipase D2 (PLD2) mRNA, complete cds                    | 3290 | 3129C>T | 3     |
| AF037335 | AF037335 | 603263 | GEN-2KJ | Homo sapiens carbonic anhydrase precursor (CA                              | 1551 | 1436G>T | 3     |

|          |          |        |         |                                                                                                |      |         |        |
|----------|----------|--------|---------|------------------------------------------------------------------------------------------------|------|---------|--------|
| AF037335 | AF037335 | 603263 | GEN-2KJ | 12) mRNA, complete cds<br>Homo sapiens carbonic anhydrase precursor (CA 12) mRNA, complete cds | 2442 | 2327C>T | 3      |
| AF038955 | AF038955 | 600874 | GEN-LEI | Homo sapiens G protein gamma 5 subunit mRNA, complete cds                                      | 490  | 453A>T  | 3      |
| AF041381 | AF041381 | 602944 | GEN-LG1 | Homo sapiens putative transcriptional repressor E2F-6 mRNA, partial cds                        | 1214 | 1214C>T | 3      |
| AF052692 | AF052692 | 603324 | GEN-MKO | Homo sapiens connexin 31 (GJB3) mRNA, complete cds                                             | 2302 | 1169A>G | 3      |
| AF052692 | AF052692 | 603324 | GEN-MKO | Homo sapiens connexin 31 (GJB3) mRNA, complete cds                                             | 2438 | 1305T>C | 3      |
| AF052692 | AF052692 | 603324 | GEN-MKO | Homo sapiens connexin 31 (GJB3) mRNA, complete cds                                             | 2504 | 1371G>C | 3      |
| AF058921 | AF058921 | None   | GEN-LJY | Homo sapiens cytosolic phospholipase A2-gamma mRNA, complete cds                               | 1972 | 1663G>A | 3      |
| AF058921 | AF058921 | None   | GEN-LJY | Homo sapiens cytosolic phospholipase A2-gamma mRNA, complete cds                               | 1989 | 1680A>T | 3      |
| AF064548 | AF064548 | 603506 | GEN-KV4 | Homo sapiens low-density lipoprotein receptor-related protein 5 (LRP5) mRNA, complete cds      | 1695 | 1647C>T | S      |
| AF064548 | AF064548 | 603506 | GEN-KV4 | Homo sapiens low-density lipoprotein receptor-related protein 5 (LRP5) mRNA, complete cds      | 4037 | 3989C>T | A1330V |
| AF064548 | AF064548 | 603506 | GEN-KV4 | Homo sapiens low-density lipoprotein receptor-related protein 5 (LRP5) mRNA, complete cds      | 4683 | 4635C>A | S      |
| AF064548 | AF064548 | 603506 | GEN-KV4 | Homo sapiens low-density lipoprotein receptor-related protein 5 (LRP5) mRNA, complete cds      | 4802 | 4754C>T | S1585L |

|          |          |        |             |                                                                   |      |         |       |
|----------|----------|--------|-------------|-------------------------------------------------------------------|------|---------|-------|
| AF084040 | AF084040 | 107940 | GEN-<br>LQ9 | Homo sapiens beta-arrestin 1A mRNA, complete cds                  | 986  | 986A>T  | E329V |
| AF084040 | AF084040 | 107940 | GEN-<br>LQ9 | Homo sapiens beta-arrestin 1A mRNA, complete cds                  | 1279 | 1279G>A | 3     |
| AJ005162 | AJ005162 | 600067 | GEN-<br>KVT | Homo sapiens mRNA for UDP-glucuronosyltransferase                 | 1915 | 1882A>C | 3     |
| AJ224538 | AJ224538 | 602741 | GEN-243     | Homo sapiens mRNA for AMP-activated protein kinase beta 2 subunit | 631  | 631C>T  | H211Y |
| D00017   | D00017   | 151740 | GEN-2D      | Lipocortin II (Annexin II)                                        | 149  | 100G>A  | D34N  |
| D00017   | D00017   | 151740 | GEN-2D      | Lipocortin II (Annexin II)                                        | 341  | 292G>T  | V98L  |
| D00017   | D00017   | 151740 | GEN-2D      | Lipocortin II (Annexin II)                                        | 479  | 430A>T  | N144Y |
| D00017   | D00017   | 151740 | GEN-2D      | Lipocortin II (Annexin II)                                        | 1288 | 1239G>A | 3     |
| ATP1A1   | D00099   | 182310 | GEN-4E8     | Homo sapiens mRNA for Na,K-ATPase alpha-subunit, complete cds     | 1059 | 741A>C  | S     |
| ATP1A1   | D00099   | 182310 | GEN-4E8     | Homo sapiens mRNA for Na,K-ATPase alpha-subunit, complete cds     | 1059 | 741A>C  | S     |
| ATP1A1   | D00099   | 182310 | GEN-4E8     | Homo sapiens mRNA for Na,K-ATPase alpha-subunit, complete cds     | 1428 | 1110G>A | S     |
| ATP1A1   | D00099   | 182310 | GEN-4E8     | Homo sapiens mRNA for Na,K-ATPase alpha-subunit, complete cds     | 2538 | 2220T>C | S     |
| ATP1A1   | D00099   | 182310 | GEN-4E8     | Homo sapiens mRNA for Na,K-ATPase alpha-subunit, complete cds     | 3324 | 3006C>T | S     |
| ATP1A1   | D00099   | 182310 | GEN-4E8     | Homo sapiens mRNA for Na,K-ATPase alpha-subunit, complete cds     | 3375 | 3057G>A | S     |
| ATP1A1   | D00099   | 182310 | GEN-4E8     | Homo sapiens mRNA for Na,K-ATPase alpha-subunit, complete cds     | 3397 | 3079G>A | 3     |
| ATP1A1   | D00099   | 182310 | GEN-4E8     | Homo sapiens mRNA for Na,K-ATPase alpha-subunit, complete cds     | 3408 | 3090C>A | 3     |

|         |        |        |         |                                                                                                          |      |         |       |
|---------|--------|--------|---------|----------------------------------------------------------------------------------------------------------|------|---------|-------|
| ATP1A1  | D00099 | 182310 | GEN-4E8 | Homo sapiens mRNA for Na,K-ATPase alpha-subunit, complete cds                                            | 3505 | 3187C>A | 3     |
| ATP1A1  | D00099 | 182310 | GEN-4E8 | Homo sapiens mRNA for Na,K-ATPase alpha-subunit, complete cds                                            | 3538 | 3220G>T | 3     |
| FECH    | D00726 | 177000 | GEN-UB  | Human mRNA for ferrochelatase (EC 4.99.1.1)                                                              | 827  | 798G>C  | S     |
| FECH    | D00726 | 177000 | GEN-UB  | Human mRNA for ferrochelatase (EC 4.99.1.1)                                                              | 1253 | 1224T>A | N408K |
| FECH    | D00726 | 177000 | GEN-UB  | Human mRNA for ferrochelatase (EC 4.99.1.1)                                                              | 1549 | 1520C>T | 3     |
| FECH    | D00726 | 177000 | GEN-UB  | Human mRNA for ferrochelatase (EC 4.99.1.1)                                                              | 1645 | 1616G>A | 3     |
| D13138  | D13138 | 179780 | GEN-1NW | Human mRNA for dipeptidase                                                                               | 566  | 523T>G  | S175A |
| CYP11B2 | D13752 | 124080 | GEN-CCD | Human CYP11B2 gene for steroid 18-hydroxylase, complete cds                                              | 1600 | 1593G>A | 3     |
| D14874  | D14874 | 103275 | GEN-1SG | Human mRNA for adrenomedullin, complete cds                                                              | 1293 | 1137A>G | 3     |
| D14874  | D14874 | 103275 | GEN-1SG | Human mRNA for adrenomedullin, complete cds                                                              | 1394 | 1238A>C | 3     |
| HADHB   | D16481 | 143450 | GEN-1Y5 | Human mRNA for mitochondrial 3-ketoacyl-CoA thiolase beta-subunit of trifunctional protein, complete cds | 871  | 825T>C  | S     |
| HADHB   | D16481 | 143450 | GEN-1Y5 | Human mRNA for mitochondrial 3-ketoacyl-CoA thiolase beta-subunit of trifunctional protein, complete cds | 1607 | 1561G>C | 3     |
| HADHB   | D16481 | 143450 | GEN-1Y5 | Human mRNA for mitochondrial 3-ketoacyl-CoA thiolase beta-subunit of trifunctional protein, complete cds | 1908 | 1862A>C | 3     |

|        |        |        |         |                                                                                                                                                                              |         |       |
|--------|--------|--------|---------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------|-------|
| HADHB  | D16481 | 143450 | GEN-1Y5 | CoA thiolase beta-subunit of trifunctional protein, complete cds<br>Human mRNA for mitochondrial 3-ketoacyl-CoA thiolase beta-subunit of trifunctional protein, complete cds | 1865A>C | 3     |
| D21243 | D21243 | 141251 | GEN-9C  | Heme oxygenase 828 (decycling) 2                                                                                                                                             | 828C>G  | S     |
| D25235 | D25235 | 104221 | GEN-3   | Adrenergic receptor alpha 1c                                                                                                                                                 | 599T>G  | I200S |
| D25235 | D25235 | 104221 | GEN-3   | Adrenergic receptor alpha 1c                                                                                                                                                 | 1039C>T | R347C |
| D25235 | D25235 | 104221 | GEN-3   | Adrenergic receptor alpha 1c                                                                                                                                                 | 1039C>T | R347C |
| D25235 | D25235 | 104221 | GEN-3   | Adrenergic receptor alpha 1c                                                                                                                                                 | 1612C>T | 3     |
| D25418 | D25418 | 600022 | GEN-78  | Prostaglandin I2 726 (prostaglandin) receptor (IP)                                                                                                                           | 635G>A  | R212H |
| D25418 | D25418 | 600022 | GEN-78  | Prostaglandin I2 1047 (prostaglandin) receptor (IP)                                                                                                                          | 956C>G  | S319W |
| D25418 | D25418 | 600022 | GEN-78  | Prostaglandin I2 1075 (prostaglandin) receptor (IP)                                                                                                                          | 984A>C  | S     |
| PTGIR  | D38128 | 600022 | GEN-4DH | Human IP gene for 203 prostacyclin receptor, exon 3                                                                                                                          | 204C>G  | 3     |
| PTGIR  | D38128 | 600022 | GEN-4DH | Human IP gene for 231 prostacyclin receptor, exon 3                                                                                                                          | 232C>A  | 3     |
| D38145 | D38145 | 601699 | GEN-4E3 | Human mRNA for 1646 prostacyclin synthase, complete cds                                                                                                                      | 1619T>C | 3     |
| D42108 | D42108 | 600597 | GEN-2U4 | Phospholipase C epsilon 1908                                                                                                                                                 | 1705G>A | V569I |
| D42108 | D42108 | 600597 | GEN-2U4 | Phospholipase C epsilon 2864                                                                                                                                                 | 2661G>A | S     |
| D42108 | D42108 | 600597 | GEN-2U4 | Phospholipase C epsilon 4453                                                                                                                                                 | 4250G>A | 3     |
| D45906 | D45906 | 601988 | GEN-2WP | Human mRNA for LIMK-2, 1323 complete cds                                                                                                                                     | 1209G>C | S     |

|        |        |        |         |                                                                           |      |         |       |
|--------|--------|--------|---------|---------------------------------------------------------------------------|------|---------|-------|
| D45906 | D45906 | 601988 | GEN-2WP | Human mRNA for LIMK-2, complete cds                                       | 1475 | 1361C>T | S454L |
| D49394 | D49394 | 182139 | GEN-5   | Serotonin 5-HT receptors 5-HT3                                            | 1914 | 1695C>G | 3     |
| D50678 | D50678 | 602600 | GEN-30Y | Human mRNA for apolipoprotein E receptor 2, complete cds                  | 3378 | 3276G>A | 3     |
| D50678 | D50678 | 602600 | GEN-30Y | Human mRNA for apolipoprotein E receptor 2, complete cds                  | 3755 | 3653G>A | 3     |
| D50678 | D50678 | 602600 | GEN-30Y | Human mRNA for apolipoprotein E receptor 2, complete cds                  | 3949 | 3847G>C | 3     |
| D50678 | D50678 | 602600 | GEN-30Y | Human mRNA for apolipoprotein E receptor 2, complete cds                  | 4368 | 4266T>A | 3     |
| D50678 | D50678 | 602600 | GEN-30Y | Human mRNA for apolipoprotein E receptor 2, complete cds                  | 4455 | 4353G>A | 3     |
| D67031 | D67031 | 601568 | GEN-3HA | Homo sapiens ADDL mRNA for adducin-like protein, complete cds             | 1441 | 1258G>A | V420M |
| D67031 | D67031 | 601568 | GEN-3HA | Homo sapiens ADDL mRNA for adducin-like protein, complete cds             | 2782 | 2599T>C | 3     |
| D87258 | D87258 | 602194 | GEN-42R | Homo sapiens mRNA for serin protease with IGF-binding motif, complete cds | 150  | 102C>T  | S     |
| D87461 | D87461 | 601931 | GEN-43N | Human mRNA for KIAA0271 gene, complete cds                                | 2432 | 2256C>A | 3     |
| D87812 | D87812 | 600528 | GEN-6   | Carnitine Palmitoyltransferase I (muscle)                                 | 2363 | 2344T>C | 3     |
| D87845 | D87845 | 602344 | GEN-44C | Human mRNA for platelet-activating factor acetylhydrolase 2, complete cds | 2299 | 2096G>A | 3     |
| D87845 | D87845 | 602344 | GEN-44C | Human mRNA for platelet-activating factor acetylhydrolase 2, complete cds | 2332 | 2129A>G | 3     |



|        |        |        |         |              |                                                |      |            |   |
|--------|--------|--------|---------|--------------|------------------------------------------------|------|------------|---|
| D89078 | D89078 | 601531 | GEN-7   | complete cds | P2Y7 purinoceptor                              | 434  | (-1284)A>T | 5 |
| D89078 | D89078 | 601531 | GEN-7   |              | P2Y7 purinoceptor                              | 889  | (-829)G>C  | 5 |
| D89078 | D89078 | 601531 | GEN-7   |              | P2Y7 purinoceptor                              | 1156 | (-562)G>C  | 5 |
| D89078 | D89078 | 601531 | GEN-7   |              | P2Y7 purinoceptor                              | 2644 | 927T>C     | S |
| D89078 | D89078 | 601531 | GEN-7   |              | P2Y7 purinoceptor                              | 2920 | 1203A>G    | 3 |
| LRP1   | D90070 | 107770 | GEN-466 |              | Human ATL-derived PMA-responsive (APR) peptide | 686  | 513T>G     | 3 |
| D90187 | D90187 | 153622 | GEN-6M  | mRNA         | Macrophage scavenger receptor 1                | 1414 | 1388T>G    | 3 |
| D90187 | D90187 | 153622 | GEN-6M  |              | Macrophage scavenger receptor 1                | 1532 | 1486A>G    | 3 |
| D90187 | D90187 | 153622 | GEN-6M  |              | Macrophage scavenger receptor 1                | 1558 | 1512G>A    | 3 |
| D90187 | D90187 | 153622 | GEN-6M  |              | Macrophage scavenger receptor 1                | 1599 | 1553A>G    | 3 |
| D90187 | D90187 | 153622 | GEN-6M  |              | Macrophage scavenger receptor 1                | 1642 | 1596T>C    | 3 |
| D90187 | D90187 | 153622 | GEN-6M  |              | Macrophage scavenger receptor 1                | 1689 | 1643G>C    | 3 |
| D90228 | D90228 | 203750 | GEN-46A |              | ACAT1                                          | 547  | 471C>A     | S |
| EDNRA  | D90348 | 131243 | GEN-4DX |              | Endothelin Receptor Type A                     | 1449 | 969C>T     | S |
| EDNRA  | D90348 | 131243 | GEN-4DX |              | Endothelin Receptor Type A                     | 1449 | 969C>T     | S |
| EDNRA  | D90348 | 131243 | GEN-4DX |              | Endothelin Receptor Type A                     | 1485 | 1005A>G    | S |
| EDNRA  | D90348 | 131243 | GEN-4DX |              | Endothelin Receptor Type A                     | 1485 | 1005A>G    | S |
| EDNRA  | D90348 | 131243 | GEN-4DX |              | Endothelin Receptor Type A                     | 1834 | 1354C>G    | 3 |
| EDNRA  | D90348 | 131243 | GEN-4DX |              | Endothelin Receptor Type A                     | 1834 | 1354C>G    | 3 |
| EDNRA  | D90348 | 131243 | GEN-4DX |              | Endothelin Receptor Type A                     | 2228 | 1748G>A    | 3 |
| EDNRA  | D90348 | 131243 | GEN-4DX |              | Endothelin Receptor Type A                     | 2376 | 1896G>A    | 3 |
| EDNRA  | D90348 | 131243 | GEN-4DX |              | Endothelin Receptor Type A                     | 2764 | 2284G>A    | 3 |

|        |        |        |                    |                                                                                                                             |       |          |        |
|--------|--------|--------|--------------------|-----------------------------------------------------------------------------------------------------------------------------|-------|----------|--------|
| EDNRA  | D90348 | 131243 | 4DX<br>GEN-<br>4DX | Endothelin Receptor Type A                                                                                                  | 2764  | 2284G>A  | 3      |
| EDNRA  | D90348 | 131243 | 4DX<br>GEN-<br>4DX | Endothelin Receptor Type A                                                                                                  | 2840  | 2360G>C  | 3      |
| EDNRA  | D90348 | 131243 | 4DX<br>GEN-<br>4DX | Endothelin Receptor Type A                                                                                                  | 2935  | 2455G>A  | 3      |
| EDNRA  | D90348 | 131243 | 4DX<br>GEN-<br>4DX | Endothelin Receptor Type A                                                                                                  | 3294  | 2814A>G  | 3      |
| FGA    | J00127 | 134820 | GEN-T3             | Human fibrinogen alpha-chain mRNA, complete cds                                                                             | 560   | 530T>A   | 1177N  |
| FGA    | J00127 | 134820 | GEN-T3             | Human fibrinogen alpha-chain mRNA, complete cds                                                                             | 1138  | 1108G>T  | A370S  |
| J00129 | J00129 | 134830 | GEN-T4             | Human fibrinogen beta-chain mRNA, partial cds                                                                               | 543   | 543C>T   | S      |
| J00129 | J00129 | 134830 | GEN-T4             | Human fibrinogen beta-chain mRNA, partial cds                                                                               | 1101  | 1101C>T  | S      |
| J00129 | J00129 | 134830 | GEN-T4             | Human fibrinogen beta-chain mRNA, partial cds                                                                               | 1409  | 1409G>A  | R470K  |
| J00137 | J00137 | 306900 | GEN-OX             | COAGULATION FACTOR IX                                                                                                       | 581   | 580A>G   | T194A  |
| J00277 | J00277 | 190020 | GEN-MH8            | Human (genomic clones lambda-[SK2-T2, HS578T]; cDNA clones RS-[3, 4, 6]) c-Ha-ras1 proto-oncogene, complete coding sequence | 81    | 81T>C    | S      |
| J02610 | J02610 | 107730 | GEN-6N             | Apolipoprotein B (including Ag(x) antigen)                                                                                  | 1931  | 1853T>C  | V618A  |
| J02610 | J02610 | 107730 | GEN-6N             | Apolipoprotein B (including Ag(x) antigen)                                                                                  | 6616  | 6538C>T  | F      |
| J02610 | J02610 | 107730 | GEN-6N             | Apolipoprotein B (including Ag(x) antigen)                                                                                  | 7014  | 6936T>C  | S      |
| J02610 | J02610 | 107730 | GEN-6N             | Apolipoprotein B (including Ag(x) antigen)                                                                                  | 7623  | 7545T>C  | S      |
| J02610 | J02610 | 107730 | GEN-6N             | Apolipoprotein B (including Ag(x) antigen)                                                                                  | 8294  | 8216C>T  | P2739L |
| J02610 | J02610 | 107730 | GEN-6N             | Apolipoprotein B (including Ag(x) antigen)                                                                                  | 8625  | 8547T>C  | S      |
| J02610 | J02610 | 107730 | GEN-6N             | Apolipoprotein B (including Ag(x) antigen)                                                                                  | 10033 | 9955G>C  | D3319H |
| J02610 | J02610 | 107730 | GEN-6N             | Apolipoprotein B (including Ag(x) antigen)                                                                                  | 10358 | 10280C>A | T3427K |

|        |        |        |         |                                                                                                                 |       |          |        |
|--------|--------|--------|---------|-----------------------------------------------------------------------------------------------------------------|-------|----------|--------|
| J02610 | J02610 | 107730 | GEN-6N  | Apolipoprotein B (including Ag(x) antigen)                                                                      | 10372 | 10294C>G | Q3432E |
| J02610 | J02610 | 107730 | GEN-6N  | Apolipoprotein B (including Ag(x) antigen)                                                                      | 11273 | 11195T>C | I3732T |
| J02610 | J02610 | 107730 | GEN-6N  | Apolipoprotein B (including Ag(x) antigen)                                                                      | 11705 | 11627C>T | A3876V |
| J02610 | J02610 | 107730 | GEN-6N  | Apolipoprotein B (including Ag(x) antigen)                                                                      | 11862 | 11784T>A | S      |
| J02610 | J02610 | 107730 | GEN-6N  | Apolipoprotein B (including Ag(x) antigen)                                                                      | 11923 | 11845T>C | F3949L |
| J02610 | J02610 | 107730 | GEN-6N  | Apolipoprotein B (including Ag(x) antigen)                                                                      | 12461 | 12383A>T | E4128V |
| J02610 | J02610 | 107730 | GEN-6N  | Apolipoprotein B (including Ag(x) antigen)                                                                      | 12476 | 12398G>C | G4133A |
| J02610 | J02610 | 107730 | GEN-6N  | Apolipoprotein B (including Ag(x) antigen)                                                                      | 12486 | 12408G>C | S      |
| J02610 | J02610 | 107730 | GEN-6N  | Apolipoprotein B (including Ag(x) antigen)                                                                      | 12619 | 12541G>A | E4181K |
| J02611 | J02611 | 107740 | GEN-6O  | Human apolipoprotein D mRNA, complete cds                                                                       | 676   | 615T>G   | 3      |
| J02611 | J02611 | 107740 | GEN-6O  | Human apolipoprotein D mRNA, complete cds                                                                       | 683   | 622T>G   | 3      |
| J02611 | J02611 | 107740 | GEN-6O  | Human apolipoprotein D mRNA, complete cds                                                                       | 701   | 640C>G   | 3      |
| J02611 | J02611 | 107740 | GEN-6O  | Human apolipoprotein D mRNA, complete cds                                                                       | 745   | 684A>G   | 3      |
| J03004 | J03004 | 139360 | GEN-79  | Guanine nucleotide binding protein (G protein), alpha inhibiting activity polypeptide 2                         | 758   | 681C>T   | S      |
| GNAI1  | J03005 | 139370 | GEN-ZI  | Human alternative guanine nucleotide-binding regulatory protein (G) alpha-inhibitory-subunit mRNA, complete cds | 1437  | 1429G>A  | 3      |
| J03019 | J03019 | 109630 | GEN-4D6 | Human beta-1-adrenergic receptor mRNA, complete cds                                                             | 503   | 417G>A   | S      |
| J03037 | J03037 | 259730 | GEN-2I  | Carbonic anhydrase II                                                                                           | 627   | 562C>T   | S      |
| J03037 | J03037 | 259730 | GEN-2I  | Carbonic anhydrase II                                                                                           | 1334  | 1269A>C  | 3      |

|        |        |        |         |                                                                       |      |          |       |
|--------|--------|--------|---------|-----------------------------------------------------------------------|------|----------|-------|
| J03037 | J03037 | 259730 | GEN-2I  | Carbonic anhydrase II                                                 | 1487 | 1422A>C  | 3     |
| J03048 | J03048 | 142290 | GEN-ZD  | Huma hemopexin mRNA, 3 end                                            | 244  | 244C>T   | R82W  |
| J03048 | J03048 | 142290 | GEN-ZD  | Huma hemopexin mRNA, 3 end                                            | 635  | 635G>A   | R212K |
| J03225 | J03225 | 152310 | GEN-ZZ  | Human lipoprotein-associated coagulation inhibitor mRNA, complete cds | 1189 | 1057G>A  | 3     |
| J03242 | J03242 | 147470 | GEN-PJ  | Insulin-like growth factor 2                                          | 932  | 380G>A   | R127H |
| J03242 | J03242 | 147470 | GEN-PJ  | Insulin-like growth factor 2                                          | 1063 | 511G>A   | A171T |
| J03242 | J03242 | 147470 | GEN-PJ  | Insulin-like growth factor 2                                          | 1190 | 638C>G   | 3     |
| J03242 | J03242 | 147470 | GEN-PJ  | Insulin-like growth factor 2                                          | 1201 | 649C>T   | 3     |
| J03250 | J03250 | 172420 | GEN-C4  | DNA topoisomerase I                                                   | 160  | (-52)C>T | 5     |
| J03250 | J03250 | 172420 | GEN-C4  | DNA topoisomerase I                                                   | 590  | 379G>A   | V127I |
| J03250 | J03250 | 172420 | GEN-C4  | DNA topoisomerase I                                                   | 1984 | 1773G>A  | S     |
| J03260 | J03260 | 139160 | GEN-7A  | Guanine nucleotide binding protein (G protein), alpha z polypeptide   | 1491 | 1479A>G  | 3     |
| J03260 | J03260 | 139160 | GEN-7A  | Guanine nucleotide binding protein (G protein), alpha z polypeptide   | 2541 | 2529T>C  | 3     |
| J03459 | J03459 | 151570 | GEN-8   | Leukotriene A4 hydrolase                                              | 140  | 72G>T    | S     |
| J03459 | J03459 | 151570 | GEN-8   | Leukotriene A4 hydrolase                                              | 1511 | 1443A>T  | E481D |
| C7     | J03507 | 217070 | GEN-11R | Human complement protein component C7 mRNA, complete cds              | 1951 | 1951G>A  | V651I |
| C7     | J03507 | 217070 | GEN-11R | Human complement protein component C7 mRNA, complete cds              | 3032 | 3032T>C  | 3     |
| C7     | J03507 | 217070 | GEN-11R | Human complement protein component C7 mRNA, complete cds              | 3634 | 3634A>G  | 3     |
| C7     | J03507 | 217070 | GEN-11R | Human complement protein component C7 mRNA, complete cds              | 3831 | 3831A>G  | 3     |
| LIPC   | J03540 | 151670 | GEN-11J | Human hepatic lipase mRNA, complete cds                               | 469  | 465T>G   | S     |
| LIPC   | J03540 | 151670 | GEN-11J | Human hepatic lipase mRNA, complete cds                               | 595  | 591A>G   | S     |

|        |        |        |         |                                                  |      |                |       |
|--------|--------|--------|---------|--------------------------------------------------|------|----------------|-------|
| LIPC   | J03540 | 151670 | GEN-11J | Human hepatic lipase mRNA, complete cds          | 648  | 644G>A         | S215N |
| LIPC   | J03540 | 151670 | GEN-11J | Human hepatic lipase mRNA, complete cds          | 817  | 813C>T         | S     |
| LIPC   | J03540 | 151670 | GEN-11J | Human hepatic lipase mRNA, complete cds          | 1441 | 1437C>A        | S     |
| J03571 | J03571 | 152390 | GEN-9   | Lipoxygenases: 5-55                              | 55   | 21C>T          | S     |
| J03571 | J03571 | 152390 | GEN-9   | lipoxigenase (leukocytes)                        | 304  | 270G>A         | S     |
| J03571 | J03571 | 152390 | GEN-9   | lipoxigenase (leukocytes)                        | 304  | 270G>A         | S     |
| J03571 | J03571 | 152390 | GEN-9   | lipoxigenase (leukocytes)                        | 959  | 925C>A         | P309T |
| J03571 | J03571 | 152390 | GEN-9   | lipoxigenase (leukocytes)                        | 1762 | 1728A>T        | S     |
| J03571 | J03571 | 152390 | GEN-9   | lipoxigenase (leukocytes)                        | 2076 | 2042-2043AC>AC | 3     |
| J03571 | J03571 | 152390 | GEN-9   | lipoxigenase (leukocytes)                        | 2076 | 2042-2043delAC | F     |
| J03571 | J03571 | 152390 | GEN-9   | lipoxigenase (leukocytes)                        | 2328 | 2294C>T        | 3     |
| J03571 | J03571 | 152390 | GEN-9   | lipoxigenase (leukocytes)                        | 2376 | 2342T>G        | 3     |
| J03853 | J03853 | 104250 | GEN-A   | lipoxigenase (leukocytes)                        | 1202 | 1164C>T        | S     |
| J03853 | J03853 | 104250 | GEN-A   | Adrenergic receptor alpha <sub>2C</sub>          | 1237 | 1199T>G        | I400S |
| J03853 | J03853 | 104250 | GEN-A   | Adrenergic receptor alpha <sub>2C</sub>          | 1372 | 1334C>G        | P445R |
| J03853 | J03853 | 104250 | GEN-A   | Adrenergic receptor alpha <sub>2C</sub>          | 1379 | 1341C>T        | S     |
| C1S    | J04080 | 120580 | GEN-13T | Complement C1S component precursor (C1 esterase) | 558  | 356G>A         | R119H |
| C1S    | J04080 | 120580 | GEN-13T | Complement C1S component precursor (C1 esterase) | 2140 | 1938A>T        | K646N |
| C1S    | J04080 | 120580 | GEN-13T | Complement C1S component precursor (C1 esterase) | 2234 | 2032A>T        | T678S |

| C1S    | J04080 | 120580 | GEN-13T | Complement C1S component precursor (C1 esterase) | 2333 | 2131G>T         | 3                   |
|--------|--------|--------|---------|--------------------------------------------------|------|-----------------|---------------------|
| J04144 | J04144 | 106180 | GEN-2L  | Angiotensin-converting enzyme (ACE)              | 501  | 479A>G          | N160S               |
| J04144 | J04144 | 106180 | GEN-2L  | Angiotensin-converting enzyme (ACE)              | 604  | 582C>T          | S                   |
| J04144 | J04144 | 106180 | GEN-2L  | Angiotensin-converting enzyme (ACE)              | 803  | 781G>T          | A261S               |
| J04144 | J04144 | 106180 | GEN-2L  | Angiotensin-converting enzyme (ACE)              | 1042 | 1020C>T         | S                   |
| J04144 | J04144 | 106180 | GEN-2L  | Angiotensin-converting enzyme (ACE)              | 1535 | 1513-1515CCT>CC | S                   |
| J04144 | J04144 | 106180 | GEN-2L  | Angiotensin-converting enzyme (ACE)              | 1535 | 1513-1515delCCT | [P505V;50 6-505del] |
| J04144 | J04144 | 106180 | GEN-2L  | Angiotensin-converting enzyme (ACE)              | 1797 | 1775A>G         | D592G               |
| J04144 | J04144 | 106180 | GEN-2L  | Angiotensin-converting enzyme (ACE)              | 2215 | 2193G>A         | S                   |
| J04144 | J04144 | 106180 | GEN-2L  | Angiotensin-converting enzyme (ACE)              | 2350 | 2328A>G         | S                   |
| J04144 | J04144 | 106180 | GEN-2L  | Angiotensin-converting enzyme (ACE)              | 2505 | 2483T>C         | M828T               |
| J04144 | J04144 | 106180 | GEN-2L  | Angiotensin-converting enzyme (ACE)              | 3409 | 3387T>C         | S                   |
| J04144 | J04144 | 106180 | GEN-2L  | Angiotensin-converting enzyme (ACE)              | 3409 | 3387T>C         | S                   |
| C6     | J05064 | 217050 | GEN-16S | Human complement component C6 mRNA, complete cds | 3281 | 3126G>A         | 3                   |
| J05096 | J05096 | 182340 | GEN-SL  | alpha-subunit of Na+/K+ ATPase isoform2          | 2364 | 2260T>G         | S754A               |
| J05096 | J05096 | 182340 | GEN-SL  | alpha-subunit of Na+/K+ ATPase isoform2          | 5295 | 5191G>A         | 3                   |
| J05158 | J05158 | 603104 | GEN-173 | Human carboxypeptidase N mRNA, 3 end             | 2314 | 2314C>T         | 3                   |
| J05158 | J05158 | 603104 | GEN-173 | Human carboxypeptidase N mRNA, 3 end             | 2316 | 2316G>T         | 3                   |
| J05158 | J05158 | 603104 | GEN-173 | Human carboxypeptidase N mRNA, 3 end             | 2332 | 2332G>T         | 3                   |

|        |        |        |         |                                                             |      |         |       |
|--------|--------|--------|---------|-------------------------------------------------------------|------|---------|-------|
| J05158 | J05158 | 603104 | GEN-173 | N mRNA, 3 end<br>Human carboxypeptidase                     | 2541 | 2541G>A | 3     |
| J05158 | J05158 | 603104 | GEN-173 | N mRNA, 3 end<br>Human carboxypeptidase                     | 2651 | 2651C>T | 3     |
| J05480 | J05480 | 114105 | GEN-D   | N mRNA, 3 end<br>Calcineurin A                              | 834  | 834A>G  | 3     |
| M6PR   | J05550 | 153618 | GEN-180 | Human mannose receptor                                      | 4890 | 4787T>A | 3     |
| J05594 | J05594 | 601688 | GEN-E   | mRNA, complete cds<br>Prostaglandin 15-OH                   | 173  | 156A>G  | S     |
| J05594 | J05594 | 601688 | GEN-E   | dehydrogenase (PGDH)<br>Prostaglandin 15-OH                 | 913  | 896C>G  | 3     |
| J05594 | J05594 | 601688 | GEN-E   | dehydrogenase (PGDH)<br>Prostaglandin 15-OH                 | 950  | 933G>A  | 3     |
| J05594 | J05594 | 601688 | GEN-E   | dehydrogenase (PGDH)<br>Prostaglandin 15-OH                 | 1448 | 1431G>A | 3     |
| J05594 | J05594 | 601688 | GEN-E   | dehydrogenase (PGDH)<br>Prostaglandin 15-OH                 | 1972 | 1955T>C | 3     |
| J05594 | J05594 | 601688 | GEN-E   | dehydrogenase (PGDH)<br>Prostaglandin 15-OH                 | 1972 | 1955T>C | 3     |
| K00396 | K00396 | 107741 | GEN-P0  | Human apolipoprotein E<br>(epsilon 2 and 3 alleles)         | 112  | 52G>A   | A18T  |
| K00396 | K00396 | 107741 | GEN-P0  | Human apolipoprotein E<br>(epsilon 2 and 3 alleles)         | 121  | 61G>A   | E21K  |
| K00396 | K00396 | 107741 | GEN-P0  | mRNA<br>Human apolipoprotein E<br>(epsilon 2 and 3 alleles) | 151  | 91G>A   | E31K  |
| K00396 | K00396 | 107741 | GEN-P0  | mRNA<br>Human apolipoprotein E<br>(epsilon 2 and 3 alleles) | 197  | 137T>C  | L46P  |
| K00396 | K00396 | 107741 | GEN-P0  | mRNA<br>Human apolipoprotein E<br>(epsilon 2 and 3 alleles) | 204  | 144delG | F     |
| K00396 | K00396 | 107741 | GEN-P0  | mRNA<br>Human apolipoprotein E<br>(epsilon 2 and 3 alleles) | 238  | 178A>G  | T60A  |
| K00396 | K00396 | 107741 | GEN-P0  | mRNA<br>Human apolipoprotein E<br>(epsilon 2 and 3 alleles) | 365  | 305C>G  | P102R |

|        |        |        |        |                                                                 |        |       |
|--------|--------|--------|--------|-----------------------------------------------------------------|--------|-------|
| K00396 | K00396 | 107741 | GEN-P0 | Human apolipoprotein E 409<br>(epsilon 2 and 3 alleles)<br>mRNA | 349G>A | A117T |
| K00396 | K00396 | 107741 | GEN-P0 | Human apolipoprotein E 448<br>(epsilon 2 and 3 alleles)<br>mRNA | 388T>C | C130R |
| K00396 | K00396 | 107741 | GEN-P0 | Human apolipoprotein E 494<br>(epsilon 2 and 3 alleles)<br>mRNA | 434G>A | G145D |
| K00396 | K00396 | 107741 | GEN-P0 | Human apolipoprotein E 515<br>(epsilon 2 and 3 alleles)<br>mRNA | 455G>A | R152Q |
| K00396 | K00396 | 107741 | GEN-P0 | Human apolipoprotein E 520<br>(epsilon 2 and 3 alleles)<br>mRNA | 460C>A | R154S |
| K00396 | K00396 | 107741 | GEN-P0 | Human apolipoprotein E 538<br>(epsilon 2 and 3 alleles)<br>mRNA | 478C>T | R160C |
| K00396 | K00396 | 107741 | GEN-P0 | Human apolipoprotein E 547<br>(epsilon 2 and 3 alleles)<br>mRNA | 487C>T | R163C |
| K00396 | K00396 | 107741 | GEN-P0 | Human apolipoprotein E 548<br>(epsilon 2 and 3 alleles)<br>mRNA | 488G>A | R163H |
| K00396 | K00396 | 107741 | GEN-P0 | Human apolipoprotein E 550<br>(epsilon 2 and 3 alleles)<br>mRNA | 490A>G | K164E |
| K00396 | K00396 | 107741 | GEN-P0 | Human apolipoprotein E 586<br>(epsilon 2 and 3 alleles)<br>mRNA | 526C>T | R176C |
| K00396 | K00396 | 107741 | GEN-P0 | Human apolipoprotein E 586<br>(epsilon 2 and 3 alleles)<br>mRNA | 526C>T | R176C |
| K00396 | K00396 | 107741 | GEN-P0 | Human apolipoprotein E 743<br>(epsilon 2 and 3 alleles)<br>mRNA | 683G>A | F     |
| K00396 | K00396 | 107741 | GEN-P0 | Human apolipoprotein E 785<br>(epsilon 2 and 3 alleles)<br>mRNA | 725G>A | R242Q |
| K00396 | K00396 | 107741 | GEN-P0 | Human apolipoprotein E 796<br>(epsilon 2 and 3 alleles)<br>mRNA | 736C>T | R246C |



|        |        |        |        |                                                                                    |         |       |
|--------|--------|--------|--------|------------------------------------------------------------------------------------|---------|-------|
| K00396 | K00396 | 107741 | GEN-P0 | Human apolipoprotein E 821<br>(epsilon 2 and 3 alleles)<br>mRNA                    | 761T>A  | V254E |
| K00396 | K00396 | 107741 | GEN-P0 | Human apolipoprotein E 865<br>(epsilon 2 and 3 alleles)<br>mRNA                    | 805C>G  | R269G |
| K00396 | K00396 | 107741 | GEN-P0 | Human apolipoprotein E 935<br>(epsilon 2 and 3 alleles)<br>mRNA                    | 875G>A  | R292H |
| K00396 | K00396 | 107741 | GEN-P0 | Human apolipoprotein E 1000<br>(epsilon 2 and 3 alleles)<br>mRNA                   | 940A>C  | S314R |
| K01911 | K01911 | 162640 | GEN-2O | Neuropeptide Y 236<br>mRNA                                                         | 150G>A  | S     |
| K01911 | K01911 | 162640 | GEN-2O | Neuropeptide Y 290<br>mRNA                                                         | 204C>T  | S     |
| AGT    | K02215 | 106150 | GEN-WK | Human angiotensinogen 659<br>mRNA, complete CDS                                    | 620C>T  | T207M |
| AGT    | K02215 | 106150 | GEN-WK | Human angiotensinogen 842<br>mRNA, complete CDS                                    | 803T>C  | M268T |
| AGT    | K02215 | 106150 | GEN-WK | Human angiotensinogen 1155<br>mRNA, complete CDS                                   | 1116G>A | S     |
| AGT    | K02215 | 106150 | GEN-WK | Human angiotensinogen 1476<br>mRNA, complete CDS                                   | 1437C>A | S     |
| AGT    | K02215 | 106150 | GEN-WK | Human angiotensinogen 1821<br>mRNA, complete CDS                                   | 1782G>A | 3     |
| AGT    | K02215 | 106150 | GEN-WK | Human angiotensinogen 2053<br>mRNA, complete CDS                                   | 2014A>C | 3     |
| K02286 | K02286 | 191840 | GEN-SQ | Human urokinase gene, 3 260<br>end                                                 | 260C>G  | A87G  |
| K02286 | K02286 | 191840 | GEN-SQ | Human urokinase gene, 3 449<br>end                                                 | 449G>C  | +150S |
| K02286 | K02286 | 191840 | GEN-SQ | Human urokinase gene, 3 887<br>end                                                 | 887A>G  | Y296C |
| K02286 | K02286 | 191840 | GEN-SQ | Human urokinase gene, 3 902<br>end                                                 | 902C>A  | P301H |
| K02286 | K02286 | 191840 | GEN-SQ | Human urokinase gene, 3 905<br>end                                                 | 905A>G  | N302S |
| KNG    | K02566 | 228960 | GEN-X2 | Human alpha-2-thiol 1248<br>proteinase inhibitor mRNA,<br>complete coding sequence | 1199C>A | T400K |
| K02765 | K02765 | 120700 | GEN-XM | Human complement 1001                                                              | 941T>C  | L314P |

|        |        |        |             |                                                                                    |      |          |        |
|--------|--------|--------|-------------|------------------------------------------------------------------------------------|------|----------|--------|
| K02765 | K02765 | 120700 | GEN-XM      | component C3 mRNA,<br>alpha and beta subunits,<br>complete cds                     | 2575 | 2515G>A  | V839I  |
| K02765 | K02765 | 120700 | GEN-XM      | Human complement<br>component C3 mRNA,<br>alpha and beta subunits,<br>complete cds | 3108 | 3048C>T  | S      |
| K02765 | K02765 | 120700 | GEN-XM      | Human complement<br>component C3 mRNA,<br>alpha and beta subunits,<br>complete cds | 3561 | 3501C>G  | S      |
| K02765 | K02765 | 120700 | GEN-XM      | Human complement<br>component C3 mRNA,<br>alpha and beta subunits,<br>complete cds | 4371 | 4311C>T  | S      |
| K02765 | K02765 | 120700 | GEN-XM      | Human complement<br>component C3 mRNA,<br>alpha and beta subunits,<br>complete cds | 4544 | 4484C>A  | P1495Q |
| K02765 | K02765 | 120700 | GEN-XM      | Human complement<br>component C3 mRNA,<br>alpha and beta subunits,<br>complete cds | 4938 | 4878T>C  | S      |
| K02765 | K02765 | 120700 | GEN-XM      | Human complement<br>component C3 mRNA,<br>alpha and beta subunits,<br>complete cds | 4956 | 4896T>C  | S      |
| K02770 | K02770 | 147720 | GEN-5M      | complete cds                                                                       | 19   | (-68)A>C | 5      |
| K02770 | K02770 | 147720 | GEN-5M      | Interleukin 1, beta                                                                | 26   | (-61)A>C | 5      |
| K02770 | K02770 | 147720 | GEN-5M      | Interleukin 1, beta                                                                | 48   | (-39)C>T | 5      |
| K02770 | K02770 | 147720 | GEN-5M      | Interleukin 1, beta                                                                | 114  | 28G>A    | E10K   |
| K02770 | K02770 | 147720 | GEN-5M      | Interleukin 1, beta                                                                | 119  | 33G>A    | M11I   |
| L00352 | L00352 | 143890 | GEN-<br>2S8 | Human low density<br>lipoprotein receptor gene,<br>exon 18                         | 71   | 72C>T    | 3      |
| L00352 | L00352 | 143890 | GEN-        | Human low density                                                                  | 103  | 104G>A   | 3      |

|        |        |        |         |                                                      |         |   |
|--------|--------|--------|---------|------------------------------------------------------|---------|---|
| L00352 | L00352 | 143890 | 2S8     | lipoprotein receptor gene, exon 18                   | 717C>T  | 3 |
| L00352 | L00352 | 143890 | GEN-2S8 | Human low density lipoprotein receptor gene, exon 18 | 882G>A  | 3 |
| L00352 | L00352 | 143890 | GEN-2S8 | Human low density lipoprotein receptor gene, exon 18 | 1181A>G | 3 |
| L00352 | L00352 | 143890 | GEN-2S8 | Human low density lipoprotein receptor gene, exon 18 | 1187C>G | 3 |
| L00352 | L00352 | 143890 | GEN-2S8 | Human low density lipoprotein receptor gene, exon 18 | 1188T>G | 3 |
| L00352 | L00352 | 143890 | GEN-2S8 | Human low density lipoprotein receptor gene, exon 18 | 1192G>A | 3 |
| L00352 | L00352 | 143890 | GEN-2S8 | Human low density lipoprotein receptor gene, exon 18 | 1223G>A | 3 |
| L00352 | L00352 | 143890 | GEN-2S8 | Human low density lipoprotein receptor gene, exon 18 | 1224C>T | 3 |
| L00352 | L00352 | 143890 | GEN-2S8 | Human low density lipoprotein receptor gene, exon 18 | 1225G>A | 3 |
| L00352 | L00352 | 143890 | GEN-2S8 | Human low density lipoprotein receptor gene, exon 18 | 1228T>C | 3 |
| L00352 | L00352 | 143890 | GEN-2S8 | Human low density lipoprotein receptor gene, exon 18 | 1235T>C | 3 |
| L00352 | L00352 | 143890 | GEN-2S8 | Human low density lipoprotein receptor gene, exon 18 | 1253A>T | 3 |
| L00352 | L00352 | 143890 | GEN-2S8 | Human low density lipoprotein receptor gene, exon 18 | 1269A>C | 3 |

|        |        |        |             |                                                            |      |         |   |
|--------|--------|--------|-------------|------------------------------------------------------------|------|---------|---|
| L00352 | L00352 | 143890 | GEN-<br>2S8 | Human low density<br>lipoprotein receptor gene,<br>exon 18 | 1268 | 1269A>T | 3 |
| L00352 | L00352 | 143890 | GEN-<br>2S8 | Human low density<br>lipoprotein receptor gene,<br>exon 18 | 1279 | 1280C>T | 3 |
| L00352 | L00352 | 143890 | GEN-<br>2S8 | Human low density<br>lipoprotein receptor gene,<br>exon 18 | 1280 | 1281G>A | 3 |
| L00352 | L00352 | 143890 | GEN-<br>2S8 | Human low density<br>lipoprotein receptor gene,<br>exon 18 | 1308 | 1309C>T | 3 |
| L00352 | L00352 | 143890 | GEN-<br>2S8 | Human low density<br>lipoprotein receptor gene,<br>exon 18 | 1309 | 1310G>A | 3 |
| L00352 | L00352 | 143890 | GEN-<br>2S8 | Human low density<br>lipoprotein receptor gene,<br>exon 18 | 1316 | 1317G>A | 3 |
| L00352 | L00352 | 143890 | GEN-<br>2S8 | Human low density<br>lipoprotein receptor gene,<br>exon 18 | 1320 | 1321T>C | 3 |
| L00352 | L00352 | 143890 | GEN-<br>2S8 | Human low density<br>lipoprotein receptor gene,<br>exon 18 | 1345 | 1346G>A | 3 |
| L00352 | L00352 | 143890 | GEN-<br>2S8 | Human low density<br>lipoprotein receptor gene,<br>exon 18 | 1368 | 1369T>C | 3 |
| L00352 | L00352 | 143890 | GEN-<br>2S8 | Human low density<br>lipoprotein receptor gene,<br>exon 18 | 1376 | 1377C>T | 3 |
| L00352 | L00352 | 143890 | GEN-<br>2S8 | Human low density<br>lipoprotein receptor gene,<br>exon 18 | 1383 | 1384C>T | 3 |
| L00352 | L00352 | 143890 | GEN-<br>2S8 | Human low density<br>lipoprotein receptor gene,<br>exon 18 | 1406 | 1407T>C | 3 |
| L00352 | L00352 | 143890 | GEN-<br>2S8 | Human low density<br>lipoprotein receptor gene,<br>exon 18 | 1418 | 1419G>C | 3 |
| L00352 | L00352 | 143890 | GEN-<br>2S8 | Human low density<br>lipoprotein receptor gene,<br>exon 18 | 1428 | 1429T>C | 3 |

|        |        |        |         |                                                         |      |                                                  |       |
|--------|--------|--------|---------|---------------------------------------------------------|------|--------------------------------------------------|-------|
| L00352 | L00352 | 143890 | GEN-2S8 | exon 18<br>Human low density lipoprotein receptor gene, | 1453 | 1454C>T                                          | 3     |
| L00352 | L00352 | 143890 | GEN-2S8 | exon 18<br>Human low density lipoprotein receptor gene, | 1796 | 1797T>C                                          | 3     |
| L00352 | L00352 | 143890 | GEN-2S8 | exon 18<br>Human low density lipoprotein receptor gene, | 2108 | 2109G>A                                          | 3     |
| L00352 | L00352 | 143890 | GEN-2S8 | exon 18<br>Human low density lipoprotein receptor gene, | 2490 | 2491A>C                                          | 3     |
| CBS    | L00972 | 236200 | GEN-UV  | exon 18<br>Human cystathionine-beta-synthase (CBS) mRNA | 1022 | 1023T>C                                          | 3     |
| CBS    | L00972 | 236200 | GEN-UV  | Human cystathionine-beta-synthase (CBS) mRNA            | 2001 | 2002C>T                                          | 3     |
| CBS    | L00972 | 236200 | GEN-UV  | Human cystathionine-beta-synthase (CBS) mRNA            | 2278 | 2279G>A                                          | 3     |
| CBS    | L00972 | 236200 | GEN-UV  | Human cystathionine-beta-synthase (CBS) mRNA            | 2358 | 2359G>C                                          | 3     |
| CBS    | L00972 | 236200 | GEN-UV  | Human cystathionine-beta-synthase (CBS) mRNA            | 2524 | 2525T>C                                          | 3     |
| CBS    | L00972 | 236200 | GEN-UV  | Human cystathionine-beta-synthase (CBS) mRNA            | 2545 | 2546C>T                                          | 3     |
| L01087 | L01087 | 600448 | GEN-CM  | Protein kinase C-theta                                  | 1940 | 1846C>A                                          | S     |
| L01087 | L01087 | 600448 | GEN-CM  | Protein kinase C-theta                                  | 1943 | 1849G>A                                          | E617K |
| L05186 | L05186 | 600758 | GEN-174 | Homo sapiens focal adhesion kinase mRNA, complete cds   | 2564 | 2550C>T                                          | S     |
| L05485 | L05485 | 178635 | GEN-MJL | Surfactant, pulmonary-associated protein D              | 921  | 918T>C                                           | S     |
| L05597 | L05597 | None   | GEN-4EV | Serotonin 5-HT receptors                                | 824  | 600T>C                                           | S     |
| L05597 | L05597 | None   | GEN-4EV | Serotonin 5-HT receptors                                | 1010 | 786*787insA [H262Q;26 ATAAATTC 2*263insl AT KFI] |       |
| EDNRB  | L06623 | 131244 | GEN-19S | Endothelin Receptor Type B                              | 88   | (-146)A>G                                        | 5     |

|        |        |        |         |                                                                                                     |      |         |       |
|--------|--------|--------|---------|-----------------------------------------------------------------------------------------------------|------|---------|-------|
| EDNRB  | L06623 | 131244 | GEN-19S | Endothelin Receptor Type B                                                                          | 332  | 99C>T   | S     |
| EDNRB  | L06623 | 131244 | GEN-19S | Endothelin Receptor Type B                                                                          | 1064 | 831G>A  | S     |
| EDNRB  | L06623 | 131244 | GEN-19S | Endothelin Receptor Type B                                                                          | 1064 | 831G>A  | S     |
| EHHADH | L07077 | 261515 | GEN-1DF | Human enoyl-CoA: hydratase 3-hydroxyacyl-CoA dehydrogenase (EHHADH) mRNA, complete cds with repeats | 1225 | 1218G>A | S     |
| EHHADH | L07077 | 261515 | GEN-1DF | Human enoyl-CoA: hydratase 3-hydroxyacyl-CoA dehydrogenase (EHHADH) mRNA, complete cds with repeats | 1823 | 1816C>A | P606T |
| ADD1   | L07261 | 102680 | GEN-1DJ | Human alpha adducin mRNA, partial cds including alternate exons A and B                             | 1852 | 1853C>G | 3     |
| TGFBR3 | L07594 | 600742 | GEN-1EA | Human transforming growth factor-beta type III receptor (TGF-beta) mRNA, complete cds               | 3966 | 3618G>C | 3     |
| L07861 | L07861 | 176977 | GEN-D0  | Protein kinase C, delta                                                                             | 445  | 387G>A  | S     |
| L07861 | L07861 | 176977 | GEN-D0  | Protein kinase C, delta                                                                             | 1835 | 1777G>A | V593M |
| CCKBR  | L08112 | 118445 | GEN-1FL | Cholecystokinin (CCKb)                                                                              | 456  | 456G>A  | S     |
| FACL1  | L09229 | 152425 | GEN-1GI | Human long-chain acyl-coenzyme A synthetase (FACL1) mRNA, complete cds                              | 3026 | 2953G>A | 3     |
| FACL1  | L09229 | 152425 | GEN-1GI | Human long-chain acyl-coenzyme A synthetase (FACL1) mRNA, complete cds                              | 3083 | 3010G>A | 3     |
| L10819 | L10819 | 171150 | GEN-LVD | Homo sapiens aryl sulfotransferase mRNA, complete cds                                               | 191  | 153C>T  | S     |
| L10819 | L10819 | 171150 | GEN-LVD | Homo sapiens aryl sulfotransferase mRNA, complete cds                                               | 200  | 162G>A  | S     |

|        |        |        |             |                                                                                                |        |       |
|--------|--------|--------|-------------|------------------------------------------------------------------------------------------------|--------|-------|
| L10819 | L10819 | 171150 | GEN-<br>LVD | complete cds<br>Homo sapiens aryl<br>sulfotransferase mRNA, 230                                | 192T>C | S     |
| L10819 | L10819 | 171150 | GEN-<br>LVD | complete cds<br>Homo sapiens aryl<br>sulfotransferase mRNA, 242                                | 204G>A | S     |
| L10819 | L10819 | 171150 | GEN-<br>LVD | complete cds<br>Homo sapiens aryl<br>sulfotransferase mRNA, 295                                | 257C>T | A86V  |
| L10819 | L10819 | 171150 | GEN-<br>LVD | complete cds<br>Homo sapiens aryl<br>sulfotransferase mRNA, 330                                | 292G>A | D98N  |
| L10819 | L10819 | 171150 | GEN-<br>LVD | complete cds<br>Homo sapiens aryl<br>sulfotransferase mRNA, 338                                | 300G>A | S     |
| L10819 | L10819 | 171150 | GEN-<br>LVD | complete cds<br>Homo sapiens aryl<br>sulfotransferase mRNA, 638                                | 600C>G | S     |
| L10819 | L10819 | 171150 | GEN-<br>LVD | complete cds<br>Homo sapiens aryl<br>sulfotransferase mRNA, 676                                | 638A>G | H213R |
| L10819 | L10819 | 171150 | GEN-<br>LVD | complete cds<br>Homo sapiens aryl<br>sulfotransferase mRNA, 940                                | 902G>A | 3     |
| L10819 | L10819 | 171150 | GEN-<br>LVD | complete cds<br>Homo sapiens aryl<br>sulfotransferase mRNA, 1011                               | 973T>C | 3     |
| C4BPB  | L11244 | 120831 | GEN-<br>1K2 | complete cds<br>Human (clone A12) C4b-<br>binding protein beta-chain<br>mRNA, complete cds 538 | 204G>A | S     |
| C4BPB  | L11244 | 120831 | GEN-<br>1K2 | complete cds<br>Human (clone A12) C4b-<br>binding protein beta-chain<br>mRNA, complete cds 796 | 462C>T | S     |
| C4BPB  | L11244 | 120831 | GEN-<br>1K2 | complete cds<br>Human (clone A12) C4b-<br>binding protein beta-chain<br>mRNA, complete cds 958 | 624C>A | S     |
| L11669 | L11669 | 102680 | GEN-<br>1KW | complete cds<br>Human tetracycline<br>transporter-like protein<br>mRNA, complete cds 544       | 424G>A | A142T |
| L11669 | L11669 | 102680 | GEN-        | complete cds<br>Human tetracycline<br>transporter-like protein<br>mRNA, complete cds 980       | 860C>T | S287L |

|        |         |        |         |                                                                                      |         |      |
|--------|---------|--------|---------|--------------------------------------------------------------------------------------|---------|------|
| L11669 | L11669  | 102680 | 1KW     | transporter-like protein mRNA, complete cds                                          | 1173G>A | S    |
|        | GEN-1KW |        |         | Human tetracycline transporter-like protein mRNA, complete cds                       |         |      |
| MDCR   | L13385  | 601545 | GEN-1O6 | Homo sapiens(clone 71) Miller-Dieker lissencephaly protein (LIS1) mRNA, complete cds | 1250C>T | 3    |
| MDCR   | L13385  | 601545 | GEN-1O6 | Homo sapiens(clone 71) Miller-Dieker lissencephaly protein (LIS1) mRNA, complete cds | 1651C>T | 3    |
| MDCR   | L13385  | 601545 | GEN-1O6 | Homo sapiens(clone 71) Miller-Dieker lissencephaly protein (LIS1) mRNA, complete cds | 1700C>T | 3    |
| MDCR   | L13385  | 601545 | GEN-1O6 | Homo sapiens(clone 71) Miller-Dieker lissencephaly protein (LIS1) mRNA, complete cds | 2745G>T | 3    |
| MDCR   | L13385  | 601545 | GEN-1O6 | Homo sapiens(clone 71) Miller-Dieker lissencephaly protein (LIS1) mRNA, complete cds | 4372G>A | 3    |
| L13436 | L13436  | 108961 | GEN-2Q  | guanylate cyclase 1410                                                               | 1411T>A | 3    |
| L13436 | L13436  | 108961 | GEN-2Q  | guanylate cyclase 1646                                                               | 1647C>G | 3    |
| L13436 | L13436  | 108961 | GEN-2Q  | guanylate cyclase 1650                                                               | 1651G>C | 3    |
| L13436 | L13436  | 108961 | GEN-2Q  | guanylate cyclase 1677                                                               | 1678C>G | 3    |
| L13436 | L13436  | 108961 | GEN-2Q  | guanylate cyclase 2222                                                               | 2223C>T | 3    |
| L13436 | L13436  | 108961 | GEN-2Q  | guanylate cyclase 2444                                                               | 2445C>T | 3    |
| L13977 | L13977  | 176785 | GEN-1PX | Human 2009 polycarboxypeptidase mRNA, complete cds                                   | 1980T>C | 3    |
| BF     | L15702  | 138470 | GEN-1UA | Human complement factor B mRNA, complete cds                                         | 95A>G   | Q32R |
| PRKCI  | L18964  | 300094 | GEN-21N | Human protein kinase C iota isoform (PRKCI) mRNA, complete cds                       | 309T>G  | S    |
| L19182 | L19182  | 602867 | GEN-    | Human MAC25 mRNA, 297                                                                | 284G>A  | R95K |



|        |        |        |                                        |                                                                           |          |       |
|--------|--------|--------|----------------------------------------|---------------------------------------------------------------------------|----------|-------|
| L19956 | L19956 | 600641 | 21Z<br>GEN-<br>LVE                     | complete cds<br>Human aryl 243<br>sulfotransferase mRNA,                  | 105A>G   | S     |
| L19956 | L19956 | 600641 | GEN-<br>LVE                            | complete cds<br>Human aryl 284<br>sulfotransferase mRNA,                  | 146C>T   | S49F  |
| L20463 | L20463 | 600445 | GEN-M                                  | complete cds<br>G-protein coupled 1671<br>adenosine A3 receptor           | 1380A>G  | 3     |
| VLDLR  | L20470 | 192977 | GEN-<br>23D                            | Human very low density 336<br>lipoprotein receptor mRNA,                  | (-56)C>T | 5     |
| VLDLR  | L20470 | 192977 | GEN-<br>23D                            | complete cds<br>Human very low density 3566<br>lipoprotein receptor mRNA, | 3175T>C  | 3     |
| L22214 | L22214 | 102775 | GEN-2S                                 | complete cds<br>Adenosine A1 receptor 557<br>(ADORA1)                     | 147G>C   | S     |
| L22214 | L22214 | 102775 | GEN-2S                                 | Adenosine A1 receptor 2622<br>(ADORA1)                                    | 2212G>A  | 3     |
| L22473 | L22473 | 600040 | GEN-<br>L9D                            | Human Bax alpha mRNA, 552<br>complete cds                                 | 552G>A   | S     |
| SLC6A3 | L24178 | 126455 | GEN-283                                | Homo sapiens dopamine 1917<br>transporter mRNA,                           | 1898C>T  | 3     |
| L24470 | L24470 | 600563 | GEN-O                                  | complete cds<br>PROSTAGLANDIN F 1422<br>RECEPTOR                          | 1185T>C  | 3     |
| L24470 | L24470 | 600563 | GEN-O                                  | PROSTAGLANDIN F 1490<br>RECEPTOR                                          | 1253C>T  | 3     |
| L24470 | L24470 | 600563 | GEN-O                                  | PROSTAGLANDIN F 1517<br>RECEPTOR                                          | 1280A>G  | 3     |
| L24470 | L24470 | 600563 | GEN-O                                  | PROSTAGLANDIN F 2244<br>RECEPTOR                                          | 2007A>G  | 3     |
| L24470 | L24470 | 600563 | GEN-O                                  | PROSTAGLANDIN F 2299<br>RECEPTOR                                          | 2062A>G  | 3     |
| L26232 | L26232 | 172425 | GEN-<br>2AK                            | Human phospholipid 906<br>transfer protein mRNA,                          | 819C>T   | S     |
| L26232 | L26232 | 172425 | GEN-<br>2AK                            | complete cds<br>Human phospholipid 1547<br>transfer protein mRNA,         | 1460C>A  | T487K |
| L27624 | L27624 | 600033 | GEN-<br>Homo sapiens tissue factor 213 | complete cds                                                              | 175C>G   | Q59E  |

|        |        |        |             |                                                                                             |         |       |
|--------|--------|--------|-------------|---------------------------------------------------------------------------------------------|---------|-------|
| L27624 | L27624 | 600033 | 2C8         | pathway inhibitor-2 mRNA,<br>complete cds                                                   | 219C>A  | S     |
| L27624 | L27624 | 600033 | GEN-<br>2C8 | Homo sapiens tissue factor<br>pathway inhibitor-2 mRNA,<br>complete cds                     | 257G>T  | C86F  |
| L27624 | L27624 | 600033 | GEN-<br>2C8 | Homo sapiens tissue factor<br>pathway inhibitor-2 mRNA,<br>complete cds                     | 396G>A  | S     |
| L27624 | L27624 | 600033 | GEN-<br>2C8 | Homo sapiens tissue factor<br>pathway inhibitor-2 mRNA,<br>complete cds                     | 398A>T  | N133I |
| L27624 | L27624 | 600033 | GEN-<br>2C8 | Homo sapiens tissue factor<br>pathway inhibitor-2 mRNA,<br>complete cds                     | 763G>A  | 3     |
| L27624 | L27624 | 600033 | GEN-<br>2C8 | Homo sapiens tissue factor<br>pathway inhibitor-2 mRNA,<br>complete cds                     | 847C>A  | 3     |
| PTGER2 | L28175 | 601586 | GEN-7C      | Prostaglandin E receptor 2<br>(subtype EP2), 53kD                                           | 159C>T  | S     |
| PTGER2 | L28175 | 601586 | GEN-7C      | Prostaglandin E receptor 2<br>(subtype EP2), 53kD                                           | 223G>A  | V75M  |
| PTGER2 | L28175 | 601586 | GEN-7C      | Prostaglandin E receptor 2<br>(subtype EP2), 53kD                                           | 1337A>G | Q446R |
| L31773 | L31773 | 104220 | GEN-<br>4DD | Adrenergic receptor alpha<br>1b                                                             | 171C>T  | S     |
| L31773 | L31773 | 104220 | GEN-<br>4DD | Adrenergic receptor alpha<br>1b                                                             | 534C>T  | S     |
| L31773 | L31773 | 104220 | GEN-<br>4DD | Adrenergic receptor alpha<br>1b                                                             | 549G>A  | S     |
| L34357 | L34357 | 600576 | GEN-<br>KV3 | Homo sapiens GATA-4<br>mRNA, complete cds                                                   | 1756T>C | 3     |
| L34357 | L34357 | 600576 | GEN-<br>KV3 | Homo sapiens GATA-4<br>mRNA, complete cds                                                   | 1893C>G | 3     |
| L36566 | L36566 | 601970 | GEN-<br>2N5 | Human helodermin-<br>preferring VIP receptor<br>(VIP2/PACAP receptor)<br>mRNA, complete cds | 1235A>G | H412R |
| L36566 | L36566 | 601970 | GEN-        | Human helodermin-<br>mRNA, complete cds                                                     | 1278A>C | S     |

|        |        |        |                                                                                         |      |           |       |
|--------|--------|--------|-----------------------------------------------------------------------------------------|------|-----------|-------|
| 2N5    |        |        | preferring VIP receptor<br>(VIP2/PACAP receptor)<br>mRNA, complete cds                  | 1092 | 1083C>T   | S     |
| NRAMP2 | L37347 | 600523 | Human integral membrane<br>protein (Nramp2) mRNA,<br>partial                            | 1092 |           |       |
| L38969 | L38969 | None   | Homo sapiens<br>thrombospondin 3<br>(THBS3) gene, complete<br>cds                       | 2968 | 2947C>T   | 3     |
| L41147 | L41147 | 601109 | Serotonin 5-HT receptors<br>5-HT6                                                       | 287  | (-181)C>T | 5     |
| L41147 | L41147 | 601109 | Serotonin 5-HT receptors<br>5-HT6                                                       | 1718 | 1251C>T   | S     |
| L48513 | L48513 | 602447 | Homo sapiens<br>paraoxonase 2 (PON2)<br>mRNA, complete cds                              | 460  | 443C>G    | A148G |
| L48513 | L48513 | 602447 | Homo sapiens<br>paraoxonase 2 (PON2)<br>mRNA, complete cds                              | 598  | 581G>A    | G194E |
| L48513 | L48513 | 602447 | Homo sapiens<br>paraoxonase 2 (PON2)<br>mRNA, complete cds                              | 949  | 932G>C    | C311S |
| L78207 | L78207 | 600509 | Cell surface receptor for<br>sulfonylureas on<br>pancreatic b cells<br>Insulin receptor | 4019 | 3981A>G   | S     |
| M10051 | M10051 | 147670 | Insulin receptor                                                                        | 2757 | 2619G>A   | S     |
| M10051 | M10051 | 147670 | Insulin receptor                                                                        | 4391 | 4253G>A   | 3     |
| M11146 | M11146 | 134770 | Human ferritin H chain<br>mRNA, complete cds                                            | 193  | 116C>T    | S39F  |
| M11146 | M11146 | 134770 | Human ferritin H chain<br>mRNA, complete cds                                            | 326  | 249T>G    | S     |
| M11146 | M11146 | 134770 | Human ferritin H chain<br>mRNA, complete cds                                            | 628  | 551A>T    | F     |
| M11146 | M11146 | 134770 | Human ferritin H chain<br>mRNA, complete cds                                            | 630  | 553G>A    | 3     |
| M11146 | M11146 | 134770 | Human ferritin H chain<br>mRNA, complete cds                                            | 652  | 575G>A    | 3     |
| FTL    | M11147 | 134790 | Human ferritin L chain<br>mRNA, complete cds                                            | 180  | 29C>A     | S10Y  |
| FTL    | M11147 | 134790 | Human ferritin L chain                                                                  | 240  | 89C>A     | T30N  |

|        |        |        |         |                                                                                  |         |       |
|--------|--------|--------|---------|----------------------------------------------------------------------------------|---------|-------|
| FTL    | M11147 | 134790 | GEN-1JZ | mRNA, complete cds                                                               | 163C>T  | S     |
|        |        |        |         | Human ferritin L chain 314                                                       |         |       |
| FTL    | M11147 | 134790 | GEN-1JZ | mRNA, complete cds                                                               | 189C>A  | F     |
|        |        |        |         | Human ferritin L chain 340                                                       |         |       |
| FTL    | M11147 | 134790 | GEN-1JZ | mRNA, complete cds                                                               | 224G>A  | G75D  |
|        |        |        |         | Human ferritin L chain 375                                                       |         |       |
| FTL    | M11147 | 134790 | GEN-1JZ | mRNA, complete cds                                                               | 600T>G  | 3     |
|        |        |        |         | Human ferritin L chain 751                                                       |         |       |
| TF     | M12530 | 190000 | GEN-1MK | mRNA, complete cds                                                               | 624G>A  | S     |
|        |        |        |         | Human transferrin mRNA, 654                                                      |         |       |
| TF     | M12530 | 190000 | GEN-1MK | complete cds                                                                     | 738C>G  | C246W |
|        |        |        |         | Human transferrin mRNA, 768                                                      |         |       |
| TF     | M12530 | 190000 | GEN-1MK | complete cds                                                                     | 1417G>T | V473F |
|        |        |        |         | Human transferrin mRNA, 1447                                                     |         |       |
| TF     | M12530 | 190000 | GEN-1MK | complete cds                                                                     | 1572G>C | S     |
|        |        |        |         | Human transferrin mRNA, 1602                                                     |         |       |
| TF     | M12530 | 190000 | GEN-1MK | complete cds                                                                     | 1602C>T | S     |
|        |        |        |         | Human transferrin mRNA, 1632                                                     |         |       |
| TF     | M12530 | 190000 | GEN-1MK | complete cds                                                                     | 1765C>T | P589S |
|        |        |        |         | Human transferrin mRNA, 1795                                                     |         |       |
| M12674 | M12674 | 133430 | GEN-7Z  | complete cds                                                                     | 975C>G  | S     |
|        |        |        |         | Estrogen receptor 1267                                                           |         |       |
| M12783 | M12783 | 190040 | GEN-QF  | Human c-sis/platelet-derived growth factor 2 (SIS/PDGF2) mRNA, complete cds      | 804T>C  | 3     |
|        |        |        |         | Human c-sis/platelet-derived growth factor 2 (SIS/PDGF2) mRNA, complete cds      |         |       |
| M12783 | M12783 | 190040 | GEN-QF  | Human c-sis/platelet-derived growth factor 2 (SIS/PDGF2) mRNA, complete cds      | 1056T>C | 3     |
|        |        |        |         | Human c-sis/platelet-derived growth factor 2 (SIS/PDGF2) mRNA, complete cds      |         |       |
| M12783 | M12783 | 190040 | GEN-QF  | Human c-sis/platelet-derived growth factor 2 (SIS/PDGF2) mRNA, complete cds      | 1158G>A | 3     |
|        |        |        |         | Human c-sis/platelet-derived growth factor 2 (SIS/PDGF2) mRNA, complete cds      |         |       |
| M13686 | M13686 | 178630 | GEN-1P1 | Human pulmonary surfactant-associated protein mRNA, complete cds, clone MPSAP-6A | 56C>T   | A19V  |
|        |        |        |         | Human pulmonary surfactant-associated protein mRNA, complete cds                 |         |       |
| M13686 | M13686 | 178630 | GEN-1P1 | Human pulmonary surfactant-associated protein mRNA, complete cds                 | 253T>C  | C85R  |
|        |        |        |         | Human pulmonary surfactant-associated protein mRNA, complete cds                 |         |       |

|        |        |        |         |                                                                                     |      |         |       |
|--------|--------|--------|---------|-------------------------------------------------------------------------------------|------|---------|-------|
| M13686 | M13686 | 178630 | GEN-1P1 | cds, clone MPSAP-6A<br>Human pulmonary surfactant-associated protein mRNA, complete | 370  | 282G>A  | S     |
| M13686 | M13686 | 178630 | GEN-1P1 | cds, clone MPSAP-6A<br>Human pulmonary surfactant-associated protein mRNA, complete | 430  | 342T>C  | S     |
| M13686 | M13686 | 178630 | GEN-1P1 | cds, clone MPSAP-6A<br>Human pulmonary surfactant-associated protein mRNA, complete | 694  | 606C>T  | S     |
| M13686 | M13686 | 178630 | GEN-1P1 | cds, clone MPSAP-6A<br>Human pulmonary surfactant-associated protein mRNA, complete | 736  | 648C>T  | S     |
| M13686 | M13686 | 178630 | GEN-1P1 | cds, clone MPSAP-6A<br>Human pulmonary surfactant-associated protein mRNA, complete | 883  | 795C>G  | 3     |
| C1NH   | M13690 | 106100 | GEN-1P6 | Human plasma protease (C1) inhibitor mRNA, complete cds                             | 1475 | 1438G>A | V480M |
| C1NH   | M13690 | 106100 | GEN-1P6 | Human plasma protease (C1) inhibitor mRNA, complete cds                             | 1595 | 1558C>T | 3     |
| C1NH   | M13690 | 106100 | GEN-1P6 | Human plasma protease (C1) inhibitor mRNA, complete cds                             | 1714 | 1677A>C | 3     |
| ALAD   | M13928 | 125270 | GEN-1Q2 | Human delta-aminolevulinate dehydratase mRNA, complete cds                          | 234  | 168T>C  | S     |
| ALAD   | M13928 | 125270 | GEN-1Q2 | Human delta-aminolevulinate dehydratase mRNA, complete cds                          | 480  | 414C>T  | S     |
| ALAD   | M13928 | 125270 | GEN-1Q2 | Human delta-aminolevulinate dehydratase mRNA, complete cds                          | 784  | 718C>T  | R240W |

|        |        |        |         |                                                                                                                         |      |            |       |
|--------|--------|--------|---------|-------------------------------------------------------------------------------------------------------------------------|------|------------|-------|
| BCL2   | M13994 | 151430 | GEN-1Q9 | complete cds<br>Human B-cell leukemia/lymphoma 2 (bcl-2) proto-oncogene mRNA encoding bcl-2-alpha protein, complete cds | 1744 | 286G>A     | A96T  |
| BCL2   | M13994 | 151430 | GEN-1Q9 | Human B-cell leukemia/lymphoma 2 (bcl-2) proto-oncogene mRNA encoding bcl-2-alpha protein, complete cds                 | 1786 | 328G>C     | G110R |
| BCL2   | M13994 | 151430 | GEN-1Q9 | Human B-cell leukemia/lymphoma 2 (bcl-2) proto-oncogene mRNA encoding bcl-2-alpha protein, complete cds                 | 2959 | 1501A>G    | 3     |
| UROD   | M14016 | 176100 | GEN-1QM | Human uroporphyrinogen decarboxylase mRNA, complete cds                                                                 | 248  | 230C>T     | P77L  |
| UROD   | M14016 | 176100 | GEN-1QM | Human uroporphyrinogen decarboxylase mRNA, complete cds                                                                 | 850  | 832G>T     | F     |
| C1R    | M14058 | 216950 | GEN-1QJ | Human complement C1r mRNA, complete cds                                                                                 | 1519 | 1456C>T    | R486C |
| M14113 | M14113 | 306700 | GEN-5T  | Factor VIII                                                                                                             | 8899 | 8728G>A    | 3     |
| ARG1   | M14502 | 207800 | GEN-1RE | Human liver arginase mRNA, complete cds                                                                                 | 800  | 744C>T     | S     |
| M14539 | M14539 | 134570 | GEN-QP  | Human factor XIII subunit a mRNA, 3 end                                                                                 | 1781 | 1781C>T    | P594L |
| M14539 | M14539 | 134570 | GEN-QP  | Human factor XIII subunit a mRNA, 3 end                                                                                 | 2041 | 2041C>G    | Q681E |
| M14539 | M14539 | 134570 | GEN-QP  | Human factor XIII subunit a mRNA, 3 end                                                                                 | 2412 | 2412C>T    | 3     |
| M14539 | M14539 | 134570 | GEN-QP  | Human factor XIII subunit a mRNA, 3 end                                                                                 | 2446 | 2446G>A    | 3     |
| M14539 | M14539 | 134570 | GEN-QP  | Human factor XIII subunit a mRNA, 3 end                                                                                 | 3282 | 3282G>T    | 3     |
| M14565 | M14565 | 118485 | GEN-30  | Cytochrome P450, subfamily XIA (cholesterol side chain cleavage)                                                        | 947  | 903G>C     | M301I |
| M15169 | M15169 | 109690 | GEN-T   | Beta2 Adrenergic Receptor                                                                                               | 466  | (-1122)C>G | 5     |

|        |        |        |         |                                              |      |            |       |
|--------|--------|--------|---------|----------------------------------------------|------|------------|-------|
| M15169 | M15169 | 109590 | GEN-T   | Beta2 Adrenergic Receptor                    | 565  | (-1023)G>A | 5     |
| M15169 | M15169 | 109590 | GEN-T   | Beta2 Adrenergic Receptor                    | 1182 | (-406)C>T  | 5     |
| M15169 | M15169 | 109590 | GEN-T   | Beta2 Adrenergic Receptor                    | 1221 | (-367)C>T  | 5     |
| M15169 | M15169 | 109590 | GEN-T   | Beta2 Adrenergic Receptor                    | 1326 | (-262)G>A  | 5     |
| M15169 | M15169 | 109590 | GEN-T   | Beta2 Adrenergic Receptor                    | 1541 | (-47)C>T   | 5     |
| M15169 | M15169 | 109590 | GEN-T   | Beta2 Adrenergic Receptor                    | 1633 | 46A>G      | R16G  |
| M15169 | M15169 | 109590 | GEN-T   | Beta2 Adrenergic Receptor                    | 1633 | 46A>G      | R16G  |
| M15169 | M15169 | 109590 | GEN-T   | Beta2 Adrenergic Receptor                    | 1666 | 79C>G      | Q27E  |
| M15169 | M15169 | 109590 | GEN-T   | Beta2 Adrenergic Receptor                    | 1666 | 79C>G      | Q27E  |
| M15169 | M15169 | 109590 | GEN-T   | Beta2 Adrenergic Receptor                    | 1666 | 79C>G      | Q27E  |
| M15169 | M15169 | 109590 | GEN-T   | Beta2 Adrenergic Receptor                    | 1687 | 100G>A     | V34M  |
| M15169 | M15169 | 109590 | GEN-T   | Beta2 Adrenergic Receptor                    | 1839 | 252G>A     | S     |
| M15169 | M15169 | 109590 | GEN-T   | Beta2 Adrenergic Receptor                    | 2110 | 523C>A     | S     |
| M15169 | M15169 | 109590 | GEN-T   | Beta2 Adrenergic Receptor                    | 2640 | 1053G>C    | S     |
| M15169 | M15169 | 109590 | GEN-T   | Beta2 Adrenergic Receptor                    | 2826 | 1239G>A    | S     |
| M15169 | M15169 | 109590 | GEN-T   | Beta2 Adrenergic Receptor                    | 2862 | 1275C>G    | 3     |
| M15169 | M15169 | 109590 | GEN-T   | Beta2 Adrenergic Receptor                    | 2864 | 1277C>A    | 3     |
| M15169 | M15169 | 109590 | GEN-T   | Beta2 Adrenergic Receptor                    | 2865 | 1278C>A    | 3     |
| M15169 | M15169 | 109590 | GEN-T   | Beta2 Adrenergic Receptor                    | 3371 | 1784A>T    | 3     |
| PCNA   | M15796 | 176740 | GEN-    | Human cyclin protein gene, complete cds      | 1063 | 945C>G     | 3     |
| DAF    | M15799 | 125240 | GEN-1UE | Human complement                             | 1160 | 1160A>C    | 3     |
|        |        |        | 1UD     | decay-accelerating factor (DAF) mRNA; 3' end |      |            |       |
| M15856 | M15856 | 238600 | GEN-33  | Lipoprotein lipase                           | 136  | (-39)T>C   | 5     |
| M15856 | M15856 | 238600 | GEN-33  | Lipoprotein lipase                           | 280  | 106G>A     | D36N  |
| M15856 | M15856 | 238600 | GEN-33  | Lipoprotein lipase                           | 438  | 264T>A     | F     |
| M15856 | M15856 | 238600 | GEN-33  | Lipoprotein lipase                           | 447  | 273G>A     | F     |
| M15856 | M15856 | 238600 | GEN-33  | Lipoprotein lipase                           | 474  | 300C>A     | F     |
| M15856 | M15856 | 238600 | GEN-33  | Lipoprotein lipase                           | 480  | 306A>C     | R102S |
| M15856 | M15856 | 238600 | GEN-33  | Lipoprotein lipase                           | 511  | 337T>C     | W113R |
| M15856 | M15856 | 238600 | GEN-33  | Lipoprotein lipase                           | 571  | 397C>T     | F     |
| M15856 | M15856 | 238600 | GEN-33  | Lipoprotein lipase                           | 680  | 506G>A     | G169E |
| M15856 | M15856 | 238600 | GEN-33  | Lipoprotein lipase                           | 722  | 548A>G     | D183G |
| M15856 | M15856 | 238600 | GEN-33  | Lipoprotein lipase                           | 770  | 596C>G     | S199C |
| M15856 | M15856 | 238600 | GEN-33  | Lipoprotein lipase                           | 781  | 607G>A     | A203T |

|        |        |        |        |                                                |      |         |       |
|--------|--------|--------|--------|------------------------------------------------|------|---------|-------|
| M15856 | M15856 | 238600 | GEN-33 | Lipoprotein lipase                             | 795  | 621C>G  | D207E |
| M15856 | M15856 | 238600 | GEN-33 | Lipoprotein lipase                             | 818  | 644G>A  | G215E |
| M15856 | M15856 | 238600 | GEN-33 | Lipoprotein lipase                             | 836  | 662T>C  | I221T |
| M15856 | M15856 | 238600 | GEN-33 | Lipoprotein lipase                             | 839  | 665G>A  | G222E |
| M15856 | M15856 | 238600 | GEN-33 | Lipoprotein lipase                             | 843  | 669C>T  | S     |
| M15856 | M15856 | 238600 | GEN-33 | Lipoprotein lipase                             | 867  | 693C>G  | D231E |
| M15856 | M15856 | 238600 | GEN-33 | Lipoprotein lipase                             | 875  | 701C>T  | P234L |
| M15856 | M15856 | 238600 | GEN-33 | Lipoprotein lipase                             | 916  | 742delG | F     |
| M15856 | M15856 | 238600 | GEN-33 | Lipoprotein lipase                             | 983  | 809G>A  | R270H |
| M15856 | M15856 | 238600 | GEN-33 | Lipoprotein lipase                             | 985  | 811T>A  | S271T |
| M15856 | M15856 | 238600 | GEN-33 | Lipoprotein lipase                             | 1003 | 829G>A  | D277N |
| M15856 | M15856 | 238600 | GEN-33 | Lipoprotein lipase                             | 1127 | 953A>G  | N318S |
| M15856 | M15856 | 238600 | GEN-33 | Lipoprotein lipase                             | 1255 | 1081G>A | A361T |
| M15856 | M15856 | 238600 | GEN-33 | Lipoprotein lipase                             | 1348 | 1174C>G | L392V |
| M15856 | M15856 | 238600 | GEN-33 | Lipoprotein lipase                             | 1401 | 1227G>A | F     |
| M15856 | M15856 | 238600 | GEN-33 | Lipoprotein lipase                             | 1508 | 1334G>A | C445Y |
| M15856 | M15856 | 238600 | GEN-33 | Lipoprotein lipase                             | 1553 | 1379C>T | A460V |
| M15856 | M15856 | 238600 | GEN-33 | Lipoprotein lipase                             | 1595 | 1421C>G | F     |
| M15856 | M15856 | 238600 | GEN-33 | Lipoprotein lipase                             | 1611 | 1437G>A | 3     |
| M15856 | M15856 | 238600 | GEN-33 | Lipoprotein lipase                             | 1973 | 1799T>C | 3     |
| M15856 | M15856 | 238600 | GEN-33 | Lipoprotein lipase                             | 2428 | 2254T>A | 3     |
| M15856 | M15856 | 238600 | GEN-33 | Lipoprotein lipase                             | 2743 | 2569T>C | 3     |
| M15856 | M15856 | 238600 | GEN-33 | Lipoprotein lipase                             | 2851 | 2677A>G | 3     |
| M15856 | M15856 | 238600 | GEN-33 | Lipoprotein lipase                             | 2851 | 2677A>G | 3     |
| M15856 | M15856 | 238600 | GEN-33 | Lipoprotein lipase                             | 2958 | 2784G>A | 3     |
| M15856 | M15856 | 238600 | GEN-33 | Lipoprotein lipase                             | 3017 | 2843T>C | 3     |
| M15856 | M15856 | 238600 | GEN-33 | Lipoprotein lipase                             | 3272 | 3098T>C | 3     |
| M15856 | M15856 | 238600 | GEN-33 | Lipoprotein lipase                             | 3272 | 3098T>C | 3     |
| M15856 | M15856 | 238600 | GEN-33 | Lipoprotein lipase                             | 3343 | 3169T>C | 3     |
| M15856 | M15856 | 238600 | GEN-33 | Lipoprotein lipase                             | 3447 | 3273C>T | 3     |
| M16006 | M16006 | 173360 | GEN-34 | Tissue Plasminogen activator inhibitor, type I | 124  | 49G>A   | V171  |
| M16006 | M16006 | 173360 | GEN-34 | Tissue Plasminogen activator inhibitor, type I | 411  | 336T>C  | S     |
| M16006 | M16006 | 173360 | GEN-34 | Tissue Plasminogen activator inhibitor, type I | 1645 | 1570T>C | 3     |



|        |        |        |             |                                                                                                                        |      |                         |       |
|--------|--------|--------|-------------|------------------------------------------------------------------------------------------------------------------------|------|-------------------------|-------|
| M16006 | M16006 | 173360 | GEN-34      | Tissue Plasminogen<br>activator inhibitor, type I                                                                      | 1974 | 189T>C                  | 3     |
| M16006 | M16006 | 173360 | GEN-34      | Tissue Plasminogen<br>activator inhibitor, type I                                                                      | 2006 | 193T>G                  | 3     |
| M16405 | M16405 | None   | GEN-<br>4ES | Muscarinic receptor, 2138<br>CHRM4                                                                                     | 2138 | 1338C>T                 | S     |
| M16405 | M16405 | None   | GEN-<br>4ES | Muscarinic receptor, 2409<br>CHRM4                                                                                     | 2409 | 1609G>A                 | 3     |
| M16538 | M16538 | 139390 | GEN-<br>1Y8 | Human signal-transducing<br>guanine nucleotide-binding<br>regulatory (G) protein beta<br>subunit mRNA, complete<br>cds | 867  | 720C>T                  | S     |
| M16538 | M16538 | 139390 | GEN-<br>1Y8 | Human signal-transducing<br>guanine nucleotide-binding<br>regulatory (G) protein beta<br>subunit mRNA, complete<br>cds | 1270 | 1123G>T                 | 3     |
| M16538 | M16538 | 139390 | GEN-<br>1Y8 | Human signal-transducing<br>guanine nucleotide-binding<br>regulatory (G) protein beta<br>subunit mRNA, complete<br>cds | 1388 | 1241C>T                 | 3     |
| M16541 | M16541 | 177400 | GEN-35      | Butyrylcholinesterase                                                                                                  | 422  | 293A>G                  | D98G  |
| M16541 | M16541 | 177400 | GEN-35      | Butyrylcholinesterase                                                                                                  | 557  | 428G>A                  | G143D |
| M16541 | M16541 | 177400 | GEN-35      | Butyrylcholinesterase                                                                                                  | 564  | 435-<br>436TT>AG>A<br>G | F146V |
| M16541 | M16541 | 177400 | GEN-35      | Butyrylcholinesterase                                                                                                  | 568  | 439C>T                  | F     |
| M16541 | M16541 | 177400 | GEN-35      | Butyrylcholinesterase                                                                                                  | 596  | 467A>G                  | Y156C |
| M16541 | M16541 | 177400 | GEN-35      | Butyrylcholinesterase                                                                                                  | 941  | 812C>T                  | T271M |
| M16541 | M16541 | 177400 | GEN-35      | Butyrylcholinesterase                                                                                                  | 961  | 832A>C                  | T278P |
| M16541 | M16541 | 177400 | GEN-35      | Butyrylcholinesterase                                                                                                  | 978  | 849G>C                  | E283D |
| M16541 | M16541 | 177400 | GEN-35      | Butyrylcholinesterase                                                                                                  | 1201 | 1072T>A                 | L358I |
| M16541 | M16541 | 177400 | GEN-35      | Butyrylcholinesterase                                                                                                  | 1306 | 1177G>A                 | G393R |
| M16541 | M16541 | 177400 | GEN-35      | Butyrylcholinesterase                                                                                                  | 1382 | 1253G>T                 | G418V |
| M16541 | M16541 | 177400 | GEN-35      | Butyrylcholinesterase                                                                                                  | 1549 | 1420T>G                 | F474V |
| M16541 | M16541 | 177400 | GEN-35      | Butyrylcholinesterase                                                                                                  | 1564 | 1435G>T                 | F     |
| M16541 | M16541 | 177400 | GEN-35      | Butyrylcholinesterase                                                                                                  | 1703 | 1574A>T                 | E525V |

|        |        |        |         |                                                           |      |          |        |
|--------|--------|--------|---------|-----------------------------------------------------------|------|----------|--------|
| M16541 | M16541 | 177400 | GEN-35  | Butyrylcholinesterase                                     | 1756 | 1627C>T  | R543C  |
| M16541 | M16541 | 177400 | GEN-35  | Butyrylcholinesterase                                     | 1828 | 1699G>A  | A567T  |
| M16541 | M16541 | 177400 | GEN-35  | Butyrylcholinesterase                                     | 1828 | 1699G>A  | A567T  |
| M16541 | M16541 | 177400 | GEN-35  | Butyrylcholinesterase                                     | 2127 | 1998A>G  | 3      |
| M16541 | M16541 | 177400 | GEN-35  | Butyrylcholinesterase                                     | 2127 | 1998A>G  | 3      |
| M16660 | M16660 | 140571 | GEN-1YC | Human 90-kDa heat-shock protein gene, cDNA, complete cds  | 825  | 741G>A   | S      |
| M16801 | M16801 | 600983 | GEN-36  | Mineralocorticoid receptor (aldosterone receptor)         | 175  | (-42)C>G | 5      |
| M16801 | M16801 | 600983 | GEN-36  | Mineralocorticoid receptor (aldosterone receptor)         | 754  | 538A>G   | I180V  |
| M16801 | M16801 | 600983 | GEN-36  | Mineralocorticoid receptor (aldosterone receptor)         | 938  | 722C>T   | A241V  |
| M16801 | M16801 | 600983 | GEN-36  | Mineralocorticoid receptor (aldosterone receptor)         | 1221 | 1005delC | F      |
| M16801 | M16801 | 600983 | GEN-36  | Mineralocorticoid receptor (aldosterone receptor)         | 1591 | 1375delT | F      |
| M16801 | M16801 | 600983 | GEN-36  | Mineralocorticoid receptor (aldosterone receptor)         | 1713 | 1497C>T  | S      |
| M16801 | M16801 | 600983 | GEN-36  | Mineralocorticoid receptor (aldosterone receptor)         | 1825 | 1609C>T  | F      |
| M16801 | M16801 | 600983 | GEN-36  | Mineralocorticoid receptor (aldosterone receptor)         | 2438 | 2222T>G  | V741G  |
| M16801 | M16801 | 600983 | GEN-36  | Mineralocorticoid receptor (aldosterone receptor)         | 2730 | 2514G>A  | S      |
| M16801 | M16801 | 600983 | GEN-36  | Mineralocorticoid receptor (aldosterone receptor)         | 5243 | 5027T>A  | 3      |
| M16801 | M16801 | 600983 | GEN-36  | Mineralocorticoid receptor (aldosterone receptor)         | 5645 | 5429G>A  | 3      |
| M16827 | M16827 | 201450 | GEN-EI  | Acyl-Coenzyme A dehydrogenase, C-4 to C-12 straight chain | 1956 | 1938T>C  | 3      |
| F5     | M16967 | 227400 | GEN-1Z8 | Human coagulation factor V mRNA, complete cds             | 2391 | 2301G>A  | S      |
| F5     | M16967 | 227400 | GEN-1Z8 | Human coagulation factor V mRNA, complete cds             | 2663 | 2573G>A  | R858K  |
| F5     | M16967 | 227400 | GEN-1Z8 | Human coagulation factor V mRNA, complete cds             | 2684 | 2594G>A  | R865H  |
| F5     | M16967 | 227400 | GEN-1Z8 | Human coagulation factor V mRNA, complete cds             | 5380 | 5290G>A  | V1764M |

|        |        |        |                |                                                                                     |      |         |       |
|--------|--------|--------|----------------|-------------------------------------------------------------------------------------|------|---------|-------|
| C8B    | M16973 | 120960 | 128<br>GEN-1ZA | V mRNA, complete cds<br>Human complement protein C8 beta subunit mRNA, complete cds | 1860 | 1833C>T | 3     |
| M17262 | M17262 | 176930 | GEN-SM         | Human prothrombin (F2) gene, complete cds, and Alu and KpnI repeats                 | 511  | 480C>T  | S     |
| C8G    | M17999 | 120930 | GEN-20Y        | Human complement component C8-gamma mRNA, complete cds                              | 193  | 132T>G  | S     |
| M18112 | M18112 | 173870 | GEN-EK         | ADP-ribosyltransferase (NAD+; poly (ADP-ribose) polymerase)                         | 2424 | 2285T>C | V762A |
| M18112 | M18112 | 173870 | GEN-EK         | ADP-ribosyltransferase (NAD+; poly (ADP-ribose) polymerase)                         | 2679 | 2540G>T | R847L |
| M18182 | M18182 | 173370 | GEN-37         | Tissue Plasminogen activator, tissue type (t-PA)                                    | 391  | 378G>A  | S     |
| M18182 | M18182 | 173370 | GEN-37         | Tissue Plasminogen activator, tissue type (t-PA)                                    | 499  | 486C>T  | S     |
| M18182 | M18182 | 173370 | GEN-37         | Tissue Plasminogen activator, tissue type (t-PA)                                    | 514  | 501C>T  | S     |
| M18182 | M18182 | 173370 | GEN-37         | Tissue Plasminogen activator, tissue type (t-PA)                                    | 1822 | 1809G>A | 3     |
| M18182 | M18182 | 173370 | GEN-37         | Tissue Plasminogen activator, tissue type (t-PA)                                    | 1977 | 1964A>G | 3     |
| M18182 | M18182 | 173370 | GEN-37         | Tissue Plasminogen activator, tissue type (t-PA)                                    | 2161 | 2148G>C | 3     |
| M20132 | M20132 | 313700 | GEN-38         | Androgen receptor (dihydrotestosterone receptor)                                    | 995  | 633G>A  | S     |
| M20132 | M20132 | 313700 | GEN-38         | Androgen receptor (dihydrotestosterone receptor)                                    | 1385 | 1023T>C | S     |
| M20132 | M20132 | 313700 | GEN-38         | Androgen receptor (dihydrotestosterone receptor)                                    | 1786 | 1424G>A | G475E |
| M20137 | M20137 | 147740 | GEN-CCJ        | Human interleukin 3 (IL-3) mRNA, complete cds, clone pcD-SR-alpha                   | 132  | 79C>T   | P27S  |
| M20560 | M20560 | 106490 | GEN-39         | Lipocortin III (Annexin III)                                                        | 1057 | 1011C>T | 3     |

|         |        |        |         |                                                                                                      |      |          |       |
|---------|--------|--------|---------|------------------------------------------------------------------------------------------------------|------|----------|-------|
| M20560  | M20560 | 106490 | GEN-39  | Lipocortin III (Annexin III)                                                                         | 1302 | 1256C>A  | 3     |
| M20566  | M20566 | 147880 | GEN-3A  | Interleukin 6A                                                                                       | 3058 | 2621A>T  | 3     |
| M21054  | M21054 | 172410 | GEN-3B  | Phospholipase A-2 (PLA-2)                                                                            | 331  | 294G>A   | S     |
|         |        |        |         | lung                                                                                                 |      |          |       |
| M21054  | M21054 | 172410 | GEN-3B  | Phospholipase A-2 (PLA-2)                                                                            | 400  | 363C>A   | D121E |
|         |        |        |         | lung                                                                                                 |      |          |       |
| CYBA    | M21186 | 233690 | GEN-24I | Human neutrophil<br>cytochrome b light chain<br>p22 phagocyte b-<br>cytochrome mRNA,<br>complete cds | 242  | 214C>T   | H72Y  |
|         |        |        |         | Human neutrophil                                                                                     | 549  |          |       |
| CYBA    | M21186 | 233690 | GEN-24I | cytochrome b light chain<br>p22 phagocyte b-<br>cytochrome mRNA,<br>complete cds                     | 549  | 521C>T   | A174V |
|         |        |        |         | Human neutrophil                                                                                     | 640  |          |       |
| CYBA    | M21186 | 233690 | GEN-24I | cytochrome b light chain<br>p22 phagocyte b-<br>cytochrome mRNA,<br>complete cds                     | 640  | 612A>G   | 3     |
|         |        |        |         | Human neutrophil                                                                                     | 665  |          |       |
| CYBA    | M21186 | 233690 | GEN-24I | cytochrome b light chain<br>p22 phagocyte b-<br>cytochrome mRNA,<br>complete cds                     | 665  | 637C>T   | 3     |
|         |        |        |         | Human neutrophil                                                                                     | 665  |          |       |
| M21616  | M21616 | 173410 | GEN-R1  | Human platelet-derived<br>growth factor (PDGF)<br>receptor mRNA, complete<br>cds                     | 4312 | 4126C>T  | 3     |
|         |        |        |         | Human platelet-derived                                                                               | 5171 |          |       |
| M21616  | M21616 | 173410 | GEN-R1  | growth factor (PDGF)<br>receptor mRNA, complete<br>cds                                               | 5171 | 4985C>A  | 3     |
|         |        |        |         | Human platelet-derived                                                                               | 5295 |          |       |
| M21616  | M21616 | 173410 | GEN-R1  | growth factor (PDGF)<br>receptor mRNA, complete<br>cds                                               | 5295 | 5109A>G  | 3     |
|         |        |        |         | Human platelet-derived                                                                               | 5295 |          |       |
| PLA2G2A | M22430 | 172411 | GEN-25V | Human RAS-F-A PLA2<br>mRNA, complete cds                                                             | 116  | (-20)G>T | 5     |
| PLA2G2A | M22430 | 172411 | GEN-    | Human RAS-F-A PLA2                                                                                   | 231  | 96G>C    | S     |

|         |        |        |               |                                             |      |                  |       |
|---------|--------|--------|---------------|---------------------------------------------|------|------------------|-------|
| PLA2G2A | M22430 | 172411 | 25V<br>GEN-   | mRNA, complete cds                          |      |                  |       |
| PLA2G2A | M22430 | 172411 | 25V<br>GEN-   | Human RASFA PLA2                            | 267  | 132C>T           | S     |
| PLA2G2A | M22430 | 172411 | 25V<br>GEN-   | mRNA, complete cds                          |      |                  |       |
| PLA2G2A | M22430 | 172411 | 25V<br>GEN-   | Human RASFA PLA2                            | 267  | 132C>T           | S     |
| PLA2G2A | M22430 | 172411 | 25V<br>GEN-   | mRNA, complete cds                          |      |                  |       |
| PLA2G2A | M22430 | 172411 | 25V<br>GEN-   | Human RASFA PLA2                            | 278  | 143-<br>144GT>GT | S     |
| PLA2G2A | M22430 | 172411 | 25V<br>GEN-   | mRNA, complete cds                          |      |                  |       |
| PLA2G2A | M22430 | 172411 | 25V<br>GEN-   | Human RASFA PLA2                            | 278  | 143-144delGT     | F     |
| PLA2G2A | M22430 | 172411 | 25V<br>GEN-   | mRNA, complete cds                          |      |                  |       |
| PLA2G2A | M22430 | 172411 | 25V<br>GEN-   | Human RASFA PLA2                            | 643  | 508C>T           | 3     |
| PLA2G2A | M22430 | 172411 | 25V<br>GEN-   | mRNA, complete cds                          |      |                  |       |
| PLA2G2A | M22430 | 172411 | 25V<br>GEN-   | Human RASFA PLA2                            | 700  | 565G>C           | 3     |
| M22613  | M22613 | 227600 | 25V<br>GEN-3C | mRNA, complete cds                          |      |                  |       |
| ATP2A2  | M23114 | 108740 | GEN-276       | COAGULATION FACTOR                          | 738  | 738C>T           | S     |
|         |        |        |               | X PRECURSOR                                 |      |                  |       |
|         |        |        |               | Homo sapiens calcium-<br>ATPase (HK1) mRNA, | 2382 | 2219C>T          | S740F |
| M24283  | M24283 | 147840 | GEN-V         | complete cds                                |      |                  |       |
| M24283  | M24283 | 147840 | GEN-V         | Intercellular adhesion<br>molecule 1        | 238  | 167A>T           | K56M  |
| M24283  | M24283 | 147840 | GEN-V         | Intercellular adhesion<br>molecule 1        | 238  | 167A>T           | K56M  |
| M24283  | M24283 | 147840 | GEN-V         | Intercellular adhesion<br>molecule 1        | 792  | 721G>A           | G241R |
| M24283  | M24283 | 147840 | GEN-V         | Intercellular adhesion<br>molecule 1        | 792  | 721G>A           | G241R |
| M24283  | M24283 | 147840 | GEN-V         | Intercellular adhesion<br>molecule 1        | 1126 | 1055C>T          | P352L |
| M24283  | M24283 | 147840 | GEN-V         | Intercellular adhesion<br>molecule 1        | 1166 | 1095C>T          | S     |
| M24283  | M24283 | 147840 | GEN-V         | Intercellular adhesion<br>molecule 1        | 1295 | 1224G>A          | S     |
| M24283  | M24283 | 147840 | GEN-V         | Intercellular adhesion<br>molecule 1        | 1476 | 1405A>G          | K469E |
| M24283  | M24283 | 147840 | GEN-V         | Intercellular adhesion<br>molecule 1        | 1476 | 1405A>G          | K469E |
| M24283  | M24283 | 147840 | GEN-V         | Intercellular adhesion<br>molecule 1        | 1476 | 1405A>G          | K469E |
| M24283  | M24283 | 147840 | GEN-V         | Intercellular adhesion<br>molecule 1        | 2043 | 1972C>T          | 3     |
| M24283  | M24283 | 147840 | GEN-V         | Intercellular adhesion<br>molecule 1        | 2043 | 1972C>T          | 3     |

|        |        |        |         |                                                                    |      |           |       |
|--------|--------|--------|---------|--------------------------------------------------------------------|------|-----------|-------|
| M24283 | M24283 | 147840 | GEN-V   | Intercellular adhesion molecule 1                                  | 2551 | 2480C>T   | 3     |
| M24283 | M24283 | 147840 | GEN-V   | Intercellular adhesion molecule 1                                  | 2681 | 2610G>A   | 3     |
| M24283 | M24283 | 147840 | GEN-V   | Intercellular adhesion molecule 1                                  | 2842 | 2771G>A   | 3     |
| M24283 | M24283 | 147840 | GEN-V   | Intercellular adhesion molecule 1                                  | 2842 | 2771G>A   | 3     |
| M24283 | M24283 | 147840 | GEN-V   | Intercellular adhesion molecule 1                                  | 2935 | 2864T>C   | 3     |
| M24283 | M24283 | 147840 | GEN-V   | Intercellular adhesion molecule 1                                  | 2938 | 2867G>A   | 3     |
| M24283 | M24283 | 147840 | GEN-V   | Intercellular adhesion molecule 1                                  | 2950 | 2879C>T   | 3     |
| CD36   | M24795 | 173510 | GEN-28R | Human CD36 antigen mRNA, complete cds                              | 79   | (-132)C>A | 5     |
| CD36   | M24795 | 173510 | GEN-28R | Human CD36 antigen mRNA, complete cds                              | 341  | 131T>G    | L44R  |
| CD36   | M24795 | 173510 | GEN-28R | Human CD36 antigen mRNA, complete cds                              | 1851 | 1641A>G   | 3     |
| M25813 | M25813 | None   | GEN-2A0 | Human unidentified gene complementary to P450c21 gene, partial cds | 1357 | 1357G>A   | V453I |
| M25813 | M25813 | None   | GEN-2A0 | Human unidentified gene complementary to P450c21 gene, partial cds | 2082 | 2082C>G   | I694M |
| M25813 | M25813 | None   | GEN-2A0 | Human unidentified gene complementary to P450c21 gene, partial cds | 2502 | 2502G>A   | 3     |
| M25813 | M25813 | None   | GEN-2A0 | Human unidentified gene complementary to P450c21 gene, partial cds | 2626 | 2626A>G   | 3     |
| M26383 | M26383 | 146930 | GEN-3E  | Interleukin 8                                                      | 259  | 185C>G    | A62G  |
| M26383 | M26383 | 146930 | GEN-3E  | Interleukin 8                                                      | 1237 | 1163A>T   | 3     |
| M26383 | M26383 | 146930 | GEN-3E  | Interleukin 8                                                      | 1281 | 1207A>G   | 3     |
| M26393 | M26393 | 201470 | GEN-EW  | Acyl-Coenzyme A dehydrogenase, C-2 to C-3 short chain              | 1797 | 1765A>G   | 3     |
| M27137 | M27137 | 109715 | GEN-5W  | 3beta hydroxysteroid dehydrogenase                                 | 1103 | 1100C>A   | T367N |

|        |        |        |         |                                                                                                                   |         |      |
|--------|--------|--------|---------|-------------------------------------------------------------------------------------------------------------------|---------|------|
| M27436 | M27436 | 134390 | GEN-R7  | Human tissue factor gene, 1414<br>complete cds, with a Alu<br>repetitive sequence in the<br>3 untranslated region | 1315C>T | 3    |
| M27436 | M27436 | 134390 | GEN-R7  | Human tissue factor gene, 1508<br>complete cds, with a Alu<br>repetitive sequence in the<br>3 untranslated region | 1409A>G | 3    |
| M27436 | M27436 | 134390 | GEN-R7  | Human tissue factor gene, 1588<br>complete cds, with a Alu<br>repetitive sequence in the<br>3 untranslated region | 1489T>G | 3    |
| M27492 | M27492 | 147810 | GEN-3F  | INTERLEUKIN 1 4686<br>RECEPTOR, TYPE I<br>PRECURSOR                                                               | 4604T>G | 3    |
| M27875 | M27875 | 107680 | GEN-2CK | Human apolipoprotein A-I 34<br>mRNA, complete cds                                                                 | 15G>C   | S    |
| M27875 | M27875 | 107680 | GEN-2CK | Human apolipoprotein A-I 202<br>mRNA, complete cds                                                                | 183C>T  | S    |
| M27875 | M27875 | 107680 | GEN-2CK | Human apolipoprotein A-I 204<br>mRNA, complete cds                                                                | 185T>G  | L62W |
| M27875 | M27875 | 107680 | GEN-2CK | Human apolipoprotein A-I 255<br>mRNA, complete cds                                                                | 236C>T  | S79F |
| M27875 | M27875 | 107680 | GEN-2CK | Human apolipoprotein A-I 689<br>mRNA, complete cds                                                                | 670C>T  | S    |
| M27875 | M27875 | 107680 | GEN-2CK | Human apolipoprotein A-I 824<br>mRNA, complete cds                                                                | 805G>A  | 3    |
| M28226 | M28226 | 158105 | GEN-R8  | Human JE gene encoding 90<br>a monocyte secretory<br>protein mRNA, complete<br>cds                                | 44C>G   | A15G |
| M28226 | M28226 | 158105 | GEN-R8  | Human JE gene encoding 151<br>a monocyte secretory<br>protein mRNA, complete<br>cds                               | 105C>T  | S    |
| M28226 | M28226 | 158105 | GEN-R8  | Human JE gene encoding 411<br>a monocyte secretory<br>protein mRNA, complete<br>cds                               | 365T>C  | 3    |
| M28614 | M28614 | 107720 | GEN-6Q  | Apolipoprotein C-III 370                                                                                          | 340C>G  | 3    |
| M28614 | M28614 | 107720 | GEN-6Q  | Apolipoprotein C-III 401                                                                                          | 371T>G  | 3    |

|        |        |        |         |                                                                                            |      |         |       |
|--------|--------|--------|---------|--------------------------------------------------------------------------------------------|------|---------|-------|
| M28614 | M28614 | 107720 | GEN-6Q  | Apolipoprotein C-III                                                                       | 479  | 449T>A  | 3     |
| CFTR   | M28668 | 602421 | GEN-2DF | Human cystic fibrosis mRNA, encoding a presumed transmembrane conductance regulator (CFTR) | 2729 | 2597G>A | C866Y |
| CFTR   | M28668 | 602421 | GEN-2DF | Human cystic fibrosis mRNA, encoding a presumed transmembrane conductance regulator (CFTR) | 5826 | 5694T>C | 3     |
| M29551 | M29551 | 114106 | GEN-F3  | SERINE/THREONINE PROTEIN PHOSPHATASE 2B CATALYTIC SUBUNIT, BETA ISOFORM                    | 936  | 820G>A  | V274M |
| M29551 | M29551 | 114106 | GEN-F3  | SERINE/THREONINE PROTEIN PHOSPHATASE 2B CATALYTIC SUBUNIT, BETA ISOFORM                    | 2640 | 2524G>A | 3     |
| M29696 | M29696 | 146661 | GEN-3H  | Interleukin 7 receptor                                                                     | 1088 | 1066G>A | V356I |
| M29882 | M29882 | 107670 | GEN-6R  | Apolipoprotein A-II                                                                        | 26   | 17C>A   | A6E   |
| M29882 | M29882 | 107670 | GEN-6R  | Apolipoprotein A-II                                                                        | 183  | 174G>A  | S     |
| M29882 | M29882 | 107670 | GEN-6R  | Apolipoprotein A-II                                                                        | 192  | 183C>A  | S     |
| CETP   | M30185 | 118470 | GEN-2FK | Human cholesteryl ester transfer protein mRNA, complete cds                                | 1283 | 1153G>C | V385L |
| CETP   | M30185 | 118470 | GEN-2FK | Human cholesteryl ester transfer protein mRNA, complete cds                                | 1298 | 1168G>C | A390P |
| CETP   | M30185 | 118470 | GEN-2FK | Human cholesteryl ester transfer protein mRNA, complete cds                                | 1394 | 1264A>G | I422V |
| CETP   | M30185 | 118470 | GEN-2FK | Human cholesteryl ester transfer protein mRNA, complete cds                                | 1394 | 1264A>G | I422V |
| CETP   | M30185 | 118470 | GEN-2FK | Human cholesteryl ester transfer protein mRNA, complete cds                                | 1506 | 1376A>G | D459G |



|         |        |        |         |                                                                                              |      |           |       |
|---------|--------|--------|---------|----------------------------------------------------------------------------------------------|------|-----------|-------|
| CETP    | M30185 | 118470 | GEN-2FK | Human cholesteryl ester transfer protein mRNA, complete cds                                  | 1696 | 1566G>A   | 3     |
| M30262  | M30262 | 600295 | GEN-WA  | Human cardiolipin-atrial natriuretic factor (CDD-ANF) mRNA, complete cds                     | 178  | 79C>T     | P27S  |
| M30262  | M30262 | 600295 | GEN-WA  | Human cardiolipin-atrial natriuretic factor (CDD-ANF) mRNA, complete cds                     | 203  | 104C>G    | A35G  |
| M30262  | M30262 | 600295 | GEN-WA  | Human cardiolipin-atrial natriuretic factor (CDD-ANF) mRNA, complete cds                     | 210  | 111G>T    | S     |
| M30262  | M30262 | 600295 | GEN-WA  | Human cardiolipin-atrial natriuretic factor (CDD-ANF) mRNA, complete cds                     | 327  | 228C>T    | S     |
| M30262  | M30262 | 600295 | GEN-WA  | Human cardiolipin-atrial natriuretic factor (CDD-ANF) mRNA, complete cds                     | 553  | 454T>C    | F     |
| M30262  | M30262 | 600295 | GEN-WA  | Human cardiolipin-atrial natriuretic factor (CDD-ANF) mRNA, complete cds                     | 626  | 527G>T    | 3     |
| M30262  | M30262 | 600295 | GEN-WA  | Human cardiolipin-atrial natriuretic factor (CDD-ANF) mRNA, complete cds                     | 640  | 541T>C    | 3     |
| M30773  | M30773 | 114106 | GEN-X   | Calcineurin B type I                                                                         | 331  | (-428)T>C | 5     |
| M30773  | M30773 | 114106 | GEN-X   | Calcineurin B type I                                                                         | 1658 | 900C>A    | 3     |
| M31145  | M31145 | 146730 | GEN-3J  | Insulin-like growth factor binding protein 1 precursor                                       | 923  | 759A>G    | I253M |
| M31145  | M31145 | 146730 | GEN-3J  | Insulin-like growth factor binding protein 1 precursor                                       | 1048 | 884T>C    | 3     |
| M31145  | M31145 | 146730 | GEN-3J  | Insulin-like growth factor binding protein 1 precursor                                       | 1260 | 1096C>G   | 3     |
| PRKAR2B | M31158 | 176912 | GEN-2GE | Human cAMP-dependent protein kinase subunit RII-beta mRNA, complete cds                      | 2790 | 2624C>G   | 3     |
| M31159  | M31159 | 146732 | GEN-2GD | Human growth hormone-dependent insulin-like growth factor-binding protein mRNA, complete cds | 204  | 95G>C     | G32A  |
| M31159  | M31159 | 146732 | GEN-    | Human growth hormone-cds                                                                     | 2178 | 2069A>T   | 3     |

|     |        |        |        |         |                                                                                       |      |         |       |
|-----|--------|--------|--------|---------|---------------------------------------------------------------------------------------|------|---------|-------|
| 2GD | M31328 | M31328 | 139130 | GEN-7G  | dependent insulin-like growth factor-binding protein mRNA, complete cds               | 1049 | 1043G>A | 3     |
|     | M32313 | M32313 | 184753 | GEN-5Y  | Guanine nucleotide binding protein (G protein), beta polypeptide 3                    | 1271 | 1241C>T | 3     |
|     | M32313 | M32313 | 184753 | GEN-5Y  | Steroid 5 alpha reductase 1                                                           | 1344 | 1314G>A | 3     |
|     | M32313 | M32313 | 184753 | GEN-5Y  | Steroid 5 alpha reductase 1                                                           | 1489 | 1459G>A | 3     |
|     | M32313 | M32313 | 184753 | GEN-5Y  | Steroid 5 alpha reductase 1                                                           | 1780 | 1750T>C | 3     |
|     | VEGF   | M32977 | 192240 | GEN-2JF | Human heparin-binding vascular endothelial growth factor (VEGF) mRNA, complete cds    | 50   | (-7)C>T | 5     |
|     | VEGF   | M32977 | 192240 | GEN-2JF | Human heparin-binding vascular endothelial growth factor (VEGF) mRNA, complete cds    | 92   | 36C>T   | S     |
|     | M33336 | M33336 | 188830 | GEN-RC  | Human cAMP-dependent protein kinase type I-alpha subunit (PRKAR1A) mRNA, complete cds | 2440 | 2353T>G | 3     |
|     | M33336 | M33336 | 188830 | GEN-RC  | Human cAMP-dependent protein kinase type I-alpha subunit (PRKAR1A) mRNA, complete cds | 2472 | 2385C>T | 3     |
|     | M33336 | M33336 | 188830 | GEN-RC  | Human cAMP-dependent protein kinase type I-alpha subunit (PRKAR1A) mRNA, complete cds | 3005 | 2918T>C | 3     |
|     | M35999 | M35999 | 173470 | GEN-Y   | Leukocyte integrin beta-3 mRNA, complete cds                                          | 53   | 35T>C   | V12A  |
|     | M35999 | M35999 | 173470 | GEN-Y   | Leukocyte integrin beta-3                                                             | 149  | 131C>A  | A44D  |
|     | M35999 | M35999 | 173470 | GEN-Y   | Leukocyte integrin beta-3                                                             | 194  | 176T>C  | L59P  |
|     | M35999 | M35999 | 173470 | GEN-Y   | Leukocyte integrin beta-3                                                             | 364  | 346C>T  | L116F |
|     | M35999 | M35999 | 173470 | GEN-Y   | Leukocyte integrin beta-3                                                             | 900  | 882T>C  | S     |

|        |        |        |         |                                                           |      |         |        |
|--------|--------|--------|---------|-----------------------------------------------------------|------|---------|--------|
| M35999 | M35999 | 173470 | GEN-Y   | Leukocyte integrin beta-3                                 | 987  | 969G>T  | E323D  |
| M35999 | M35999 | 173470 | GEN-Y   | Leukocyte integrin beta-3                                 | 1161 | 1143C>A | S      |
| M35999 | M35999 | 173470 | GEN-Y   | Leukocyte integrin beta-3                                 | 1161 | 1143C>A | S      |
| M35999 | M35999 | 173470 | GEN-Y   | Leukocyte integrin beta-3                                 | 1551 | 1533G>A | S      |
| M35999 | M35999 | 173470 | GEN-Y   | Leukocyte integrin beta-3                                 | 1551 | 1533G>A | S      |
| M35999 | M35999 | 173470 | GEN-Y   | Leukocyte integrin beta-3                                 | 1562 | 1544G>A | R515Q  |
| M35999 | M35999 | 173470 | GEN-Y   | Leukocyte integrin beta-3                                 | 1563 | 1545G>A | S      |
| M35999 | M35999 | 173470 | GEN-Y   | Leukocyte integrin beta-3                                 | 1563 | 1545G>A | S      |
| M35999 | M35999 | 173470 | GEN-Y   | Leukocyte integrin beta-3                                 | 2226 | 2208C>T | S      |
| M35999 | M35999 | 173470 | GEN-Y   | Leukocyte integrin beta-3                                 | 2426 | 2408G>C | 3      |
| M35999 | M35999 | 173470 | GEN-Y   | Leukocyte integrin beta-3                                 | 3056 | 3038C>T | 3      |
| M35999 | M35999 | 173470 | GEN-Y   | Leukocyte integrin beta-3                                 | 3098 | 3080A>G | 3      |
| M35999 | M35999 | 173470 | GEN-Y   | Leukocyte integrin beta-3                                 | 3403 | 3385A>T | 3      |
| M35999 | M35999 | 173470 | GEN-Y   | Leukocyte integrin beta-3                                 | 3927 | 3909C>T | 3      |
| PLCG2  | M37238 | 600220 | GEN-2O1 | Phospholipase C gamma-2                                   | 449  | 297A>G  | S      |
| PLCG2  | M37238 | 600220 | GEN-2O1 | Phospholipase C gamma-2                                   | 883  | 731A>G  | H244R  |
| PLCG2  | M37238 | 600220 | GEN-2O1 | Phospholipase C gamma-2                                   | 922  | 770A>T  | H257L  |
| PLCG2  | M37238 | 600220 | GEN-2O1 | Phospholipase C gamma-2                                   | 954  | 802C>T  | R268W  |
| PLCG2  | M37238 | 600220 | GEN-2O1 | Phospholipase C gamma-2                                   | 1301 | 1149T>C | S      |
| PLCG2  | M37238 | 600220 | GEN-2O1 | Phospholipase C gamma-2                                   | 1649 | 1497T>C | S      |
| PLCG2  | M37238 | 600220 | GEN-2O1 | Phospholipase C gamma-2                                   | 2666 | 2514G>A | S      |
| PLCG2  | M37238 | 600220 | GEN-2O1 | Phospholipase C gamma-2                                   | 3245 | 3093C>T | S      |
| PLCG2  | M37238 | 600220 | GEN-2O1 | Phospholipase C gamma-2                                   | 3245 | 3093C>T | S      |
| PLCG2  | M37238 | 600220 | GEN-2O1 | Phospholipase C gamma-2                                   | 3436 | 3284G>A | G1095D |
| PLCG2  | M37238 | 600220 | GEN-2O1 | Phospholipase C gamma-2                                   | 4207 | 4055C>G | 3      |
| PAM    | M37721 | 170270 | GEN-2OK | Human peptidylglycine alpha-amidating monooxygenase mRNA, | 3183 | 2995T>A | 3      |

|        |        |        |         |                                                                                |      |         |       |
|--------|--------|--------|---------|--------------------------------------------------------------------------------|------|---------|-------|
| PAM    | M37721 | 170270 | GEN-2OK | Human peptidylglycine alpha-amidating monooxygenase mRNA, complete cds         | 3530 | 3342A>G | 3     |
| M37825 | M37825 | 165190 | GEN-2OM | Human fibroblast growth factor-5 (FGF-5) mRNA, complete cds                    | 787  | 648T>G  | S     |
| M54968 | M54968 | 190070 | GEN-35G | Human K-ras oncogene protein mRNA, complete cds                                | 711  | 519T>C  | S     |
| M54968 | M54968 | 190070 | GEN-35G | Human K-ras oncogene protein mRNA, complete cds                                | 936  | 744G>T  | 3     |
| M54968 | M54968 | 190070 | GEN-35G | Human K-ras oncogene protein mRNA, complete cds                                | 1270 | 1078T>C | 3     |
| M54968 | M54968 | 190070 | GEN-35G | Human K-ras oncogene protein mRNA, complete cds                                | 3268 | 3076T>G | 3     |
| M54968 | M54968 | 190070 | GEN-35G | Human K-ras oncogene protein mRNA, complete cds                                | 4529 | 4337A>C | 3     |
| M54968 | M54968 | 190070 | GEN-35G | Human K-ras oncogene protein mRNA, complete cds                                | 4555 | 4363A>G | 3     |
| M54968 | M54968 | 190070 | GEN-35G | Human K-ras oncogene protein mRNA, complete cds                                | 4672 | 4480A>C | 3     |
| M55040 | M55040 | 100740 | GEN-3Q  | acetylcholinesterase                                                           | 323  | 167C>T  | P56L  |
| M55040 | M55040 | 100740 | GEN-3Q  | acetylcholinesterase                                                           | 1154 | 998T>A  | V333E |
| M55040 | M55040 | 100740 | GEN-3Q  | acetylcholinesterase                                                           | 1213 | 1057C>A | H353N |
| M55040 | M55040 | 100740 | GEN-3Q  | acetylcholinesterase                                                           | 1482 | 1326G>T | S     |
| M55040 | M55040 | 100740 | GEN-3Q  | acetylcholinesterase                                                           | 1587 | 1431C>T | S     |
| M55040 | M55040 | 100740 | GEN-3Q  | acetylcholinesterase                                                           | 1587 | 1431C>T | S     |
| M55040 | M55040 | 100740 | GEN-3Q  | acetylcholinesterase                                                           | 1663 | 1507T>C | F503L |
| M55040 | M55040 | 100740 | GEN-3Q  | Human 47-kD autosomal chronic granulomatous disease protein mRNA, complete cds | 291  | 269G>A  | R90H  |
| NCF1   | M55067 | 233700 | GEN-35R |                                                                                |      |         |       |

|      |        |        |             |                                                                                         |      |         |       |
|------|--------|--------|-------------|-----------------------------------------------------------------------------------------|------|---------|-------|
| NCF1 | M55067 | 233700 | GEN-<br>35R | Human 47-kD autosomal<br>chronic granulomatous<br>disease protein mRNA,<br>complete cds | 367  | 345C>T  | S     |
| NCF1 | M55067 | 233700 | GEN-<br>35R | Human 47-kD autosomal<br>chronic granulomatous<br>disease protein mRNA,<br>complete cds | 409  | 387G>A  | S     |
| NCF1 | M55067 | 233700 | GEN-<br>35R | Human 47-kD autosomal<br>chronic granulomatous<br>disease protein mRNA,<br>complete cds | 518  | 496G>A  | D166N |
| NCF1 | M55067 | 233700 | GEN-<br>35R | Human 47-kD autosomal<br>chronic granulomatous<br>disease protein mRNA,<br>complete cds | 580  | 558G>A  | S     |
| NCF1 | M55067 | 233700 | GEN-<br>35R | Human 47-kD autosomal<br>chronic granulomatous<br>disease protein mRNA,<br>complete cds | 847  | 825T>C  | S     |
| NCF1 | M55067 | 233700 | GEN-<br>35R | Human 47-kD autosomal<br>chronic granulomatous<br>disease protein mRNA,<br>complete cds | 871  | 849G>A  | S     |
| NCF1 | M55067 | 233700 | GEN-<br>35R | Human 47-kD autosomal<br>chronic granulomatous<br>disease protein mRNA,<br>complete cds | 930  | 908C>T  | S303L |
| NCF1 | M55067 | 233700 | GEN-<br>35R | Human 47-kD autosomal<br>chronic granulomatous<br>disease protein mRNA,<br>complete cds | 945  | 923C>T  | A308V |
| NCF1 | M55067 | 233700 | GEN-<br>35R | Human 47-kD autosomal<br>chronic granulomatous<br>disease protein mRNA,<br>complete cds | 958  | 936T>C  | S     |
| NCF1 | M55067 | 233700 | GEN-<br>35R | Human 47-kD autosomal<br>chronic granulomatous<br>disease protein mRNA,<br>complete cds | 966  | 944C>T  | S315L |
| NCF1 | M55067 | 233700 | GEN-<br>35R | Human 47-kD autosomal<br>chronic granulomatous<br>disease protein mRNA,<br>complete cds | 1024 | 1002G>A | S     |

|        |        |        |         |                                                                                |      |         |       |
|--------|--------|--------|---------|--------------------------------------------------------------------------------|------|---------|-------|
| NCF1   | M55067 | 233700 | 35R     | chronic granulomatous disease protein mRNA, complete cds                       | 1089 | 1067C>A | T356K |
| NCF1   | M55067 | 233700 | GEN-35R | Human 47-kD autosomal chronic granulomatous disease protein mRNA, complete cds | 1098 | 1076C>T | S359F |
| NCF1   | M55067 | 233700 | GEN-35R | Human 47-kD autosomal chronic granulomatous disease protein mRNA, complete cds | 1250 | 1228C>T | 3     |
| M55643 | M55643 | 164011 | GEN-RP  | Human factor KBF1 mRNA, complete cds                                           | 1936 | 1755G>A | S     |
| M57899 | M57899 | 191740 | GEN-38A | Human bilirubin UDP-glucuronosyltransferase isozyme 1 mRNA, complete cds       | 1828 | 1813C>T | 3     |
| M57899 | M57899 | 191740 | GEN-38A | Human bilirubin UDP-glucuronosyltransferase isozyme 1 mRNA, complete cds       | 1956 | 1941C>G | 3     |
| M57899 | M57899 | 191740 | GEN-38A | Human bilirubin UDP-glucuronosyltransferase isozyme 1 mRNA, complete cds       | 2057 | 2042C>G | 3     |
| MYH7   | M58018 | 160760 | GEN-38J | Homo sapiens beta-myosin heavy chain (MYH7) mRNA, complete cds                 | 407  | 321T>G  | D107E |
| MYH7   | M58018 | 160760 | GEN-38J | Homo sapiens beta-myosin heavy chain (MYH7) mRNA, complete cds                 | 818  | 732C>T  | S     |
| MYH7   | M58018 | 160760 | GEN-38J | Homo sapiens beta-myosin heavy chain (MYH7) mRNA, complete cds                 | 2132 | 2046C>G | S     |
| MYH7   | M58018 | 160760 | GEN-38J | Homo sapiens beta-myosin heavy chain (MYH7) mRNA, complete cds                 | 2837 | 2751T>C | S     |

|        |        |        |         |                                                                                         |      |                       |        |
|--------|--------|--------|---------|-----------------------------------------------------------------------------------------|------|-----------------------|--------|
| MYH7   | M58018 | 160760 | GEN-38J | Homo sapiens beta-myosin heavy chain (MYH7) mRNA, complete cds                          | 2913 | 2827T>C               | S      |
| MYH7   | M58018 | 160760 | GEN-38J | Homo sapiens beta-myosin heavy chain (MYH7) mRNA, complete cds                          | 3300 | 3214G>T               | D1072Y |
| MYH7   | M58018 | 160760 | GEN-38J | Homo sapiens beta-myosin heavy chain (MYH7) mRNA, complete cds                          | 3456 | 3370T>G               | S1124A |
| MYH7   | M58018 | 160760 | GEN-38J | Homo sapiens beta-myosin heavy chain (MYH7) mRNA, complete cds                          | 5507 | 5421C>G               | S      |
| M58525 | M58525 | 116790 | GEN-3S  | Catechol-O- methyltransferase                                                           | 390  | 186T>C                | S      |
| M58525 | M58525 | 116790 | GEN-3S  | Catechol-O- methyltransferase                                                           | 390  | 186T>C                | S      |
| M58525 | M58525 | 116790 | GEN-3S  | Catechol-O- methyltransferase                                                           | 418  | 214G>T                | A72S   |
| M58525 | M58525 | 116790 | GEN-3S  | Catechol-O- methyltransferase                                                           | 423  | 219G>A                | S      |
| M58525 | M58525 | 116790 | GEN-3S  | Catechol-O- methyltransferase                                                           | 612  | 408C>G                | S      |
| M58525 | M58525 | 116790 | GEN-3S  | Catechol-O- methyltransferase                                                           | 676  | 472A>G                | M158V  |
| M58525 | M58525 | 116790 | GEN-3S  | Catechol-O- methyltransferase                                                           | 676  | 472A>G                | M158V  |
| M58525 | M58525 | 116790 | GEN-3S  | Catechol-O- methyltransferase                                                           | 813  | 609C>T                | S      |
| M58525 | M58525 | 116790 | GEN-3S  | Catechol-O- methyltransferase                                                           | 1031 | 827delC               | F      |
| M58525 | M58525 | 116790 | GEN-3S  | Catechol-O- methyltransferase                                                           | 1039 | 835C>A                | 3      |
| M59305 | M59305 | 108962 | GEN-39P | Human atrial natriuretic peptide clearance receptor (ANP C-receptor) mRNA, complete cds | 160  | (-203)-(-199)delTTTTT | F      |
| M59979 | M59979 | 176805 | GEN-Z   | Cyclooxygenase 1 COX1                                                                   | 644  | 639C>A                | S      |
| M59979 | M59979 | 176805 | GEN-Z   | Cyclooxygenase 1 COX1                                                                   | 1892 | 1887C>A               | 3      |
| M59979 | M59979 | 176805 | GEN-Z   | Cyclooxygenase 1 COX1                                                                   | 2030 | 2025G>A               | 3      |
| M60335 | M60335 | 192225 | GEN-3U  | Vascular cell adhesion molecule 1                                                       | 1562 | 1463A>G               | H488R  |

|        |        |        |         |                                                     |      |           |   |
|--------|--------|--------|---------|-----------------------------------------------------|------|-----------|---|
| M60335 | M60335 | 192225 | GEN-3U  | Vascular cell adhesion molecule 1                   | 2178 | 2079C>T   | S |
| M60335 | M60335 | 192225 | GEN-3U  | Vascular cell adhesion molecule 1                   | 2178 | 2079C>T   | S |
| M60335 | M60335 | 192225 | GEN-3U  | Vascular cell adhesion molecule 1                   | 2196 | 2097T>C   | S |
| M60335 | M60335 | 192225 | GEN-3U  | Vascular cell adhesion molecule 1                   | 2307 | 2208A>G   | S |
| M60335 | M60335 | 192225 | GEN-3U  | Vascular cell adhesion molecule 1                   | 2321 | 2222T>C   | 3 |
| FGF7   | M60828 | 148180 | GEN-3BE | Human keratinocyte growth factor mRNA, complete cds | 323  | (-123)G>C | 5 |
| FGF7   | M60828 | 148180 | GEN-3BE | Human keratinocyte growth factor mRNA, complete cds | 1180 | 735T>C    | 3 |
| FGF7   | M60828 | 148180 | GEN-3BE | Human keratinocyte growth factor mRNA, complete cds | 1201 | 756A>G    | 3 |
| FGF7   | M60828 | 148180 | GEN-3BE | Human keratinocyte growth factor mRNA, complete cds | 1216 | 771A>G    | 3 |
| FGF7   | M60828 | 148180 | GEN-3BE | Human keratinocyte growth factor mRNA, complete cds | 1218 | 773G>C    | 3 |
| FGF7   | M60828 | 148180 | GEN-3BE | Human keratinocyte growth factor mRNA, complete cds | 1266 | 821A>C    | 3 |
| FGF7   | M60828 | 148180 | GEN-3BE | Human keratinocyte growth factor mRNA, complete cds | 1306 | 861C>T    | 3 |
| FGF7   | M60828 | 148180 | GEN-3BE | Human keratinocyte growth factor mRNA, complete cds | 1654 | 1209A>T   | 3 |
| FGF7   | M60828 | 148180 | GEN-3BE | Human keratinocyte growth factor mRNA, complete cds | 1657 | 1212T>C   | 3 |
| FGF7   | M60828 | 148180 | GEN-3BE | Human keratinocyte growth factor mRNA, complete cds | 1799 | 1354A>T   | 3 |
| FGF7   | M60828 | 148180 | GEN-3BE | Human keratinocyte growth factor mRNA, complete cds | 1801 | 1356C>T   | 3 |



|         |        |        |     |                                                                                         |      |         |   |
|---------|--------|--------|-----|-----------------------------------------------------------------------------------------|------|---------|---|
| FGF7    | M60828 | 148180 | 3BE | growth factor mRNA,<br>complete cds                                                     |      |         |   |
| GEN-3BE |        |        |     | Human keratinocyte<br>growth factor mRNA,                                               | 1867 | 1422A>G | 3 |
| FGF7    | M60828 | 148180 | 3BE | complete cds                                                                            |      |         |   |
| GEN-3BE |        |        |     | Human keratinocyte<br>growth factor mRNA,                                               | 1945 | 1500C>A | 3 |
| FGF7    | M60828 | 148180 | 3BE | complete cds                                                                            |      |         |   |
| GEN-3BE |        |        |     | Human keratinocyte<br>growth factor mRNA,                                               | 1973 | 1528G>A | 3 |
| FGF7    | M60828 | 148180 | 3BE | complete cds                                                                            |      |         |   |
| GEN-3BE |        |        |     | Human keratinocyte<br>growth factor mRNA,                                               | 2167 | 1722G>A | 3 |
| FGF7    | M60828 | 148180 | 3BE | complete cds                                                                            |      |         |   |
| GEN-3BE |        |        |     | Human keratinocyte<br>growth factor mRNA,                                               | 2186 | 1741A>G | 3 |
| FGF7    | M60828 | 148180 | 3BE | complete cds                                                                            |      |         |   |
| GEN-3BE |        |        |     | Human keratinocyte<br>growth factor mRNA,                                               | 2302 | 1857T>A | 3 |
| FGF7    | M60828 | 148180 | 3BE | complete cds                                                                            |      |         |   |
| GEN-3BE |        |        |     | Human keratinocyte<br>growth factor mRNA,                                               | 2328 | 1883G>A | 3 |
| IGFBP4  | M62403 | 146733 | 3CJ | Human insulin-like growth<br>factor binding protein 4<br>(IGFBP4) mRNA, complete<br>cds | 859  | 776G>A  | S |
| IGFBP4  | M62403 | 146733 | 3CJ | Human insulin-like growth<br>factor binding protein 4<br>(IGFBP4) mRNA, complete<br>cds | 1403 | 1320G>T | 3 |
| IGFBP4  | M62403 | 146733 | 3CJ | Human insulin-like growth<br>factor binding protein 4<br>(IGFBP4) mRNA, complete<br>cds | 1443 | 1360G>A | 3 |
| IGFBP4  | M62403 | 146733 | 3CJ | Human insulin-like growth<br>factor binding protein 4<br>(IGFBP4) mRNA, complete<br>cds | 1446 | 1363G>A | 3 |
| IGFBP4  | M62403 | 146733 | 3CJ | Human insulin-like growth<br>factor binding protein 4<br>cds                            | 1485 | 1402A>T | 3 |

|        |        |        |         |                             |                                                                                          |      |         |       |
|--------|--------|--------|---------|-----------------------------|------------------------------------------------------------------------------------------|------|---------|-------|
| M62424 | M62424 | 187930 | GEN-3W  | (IGFBP4) mRNA, complete cds | Coagulation factor II (thrombin) receptor                                                | 3210 | 2986C>T | 3     |
| M62424 | M62424 | 187930 | GEN-3W  |                             | Coagulation factor II (thrombin) receptor                                                | 3211 | 2987G>A | 3     |
| M62424 | M62424 | 187930 | GEN-3W  |                             | Coagulation factor II (thrombin) receptor                                                | 3247 | 3023T>C | 3     |
| M62782 | M62782 | 146734 | GEN-3CU |                             | Homo sapiens insulin-like growth factor binding protein 5 (IGFBP-5) mRNA, complete cds   | 908  | 852C>T  | 3     |
| APOH   | M62839 | 138700 | GEN-3CY |                             | Human apolipoprotein H mRNA, complete cds                                                | 500  | 461G>A  | R154H |
| APOH   | M62839 | 138700 | GEN-3CY |                             | Human apolipoprotein H mRNA, complete cds                                                | 835  | 796G>T  | V266L |
| APOH   | M62839 | 138700 | GEN-3CY |                             | Human apolipoprotein H mRNA, complete cds                                                | 1098 | 1059T>C | 3     |
| M63012 | M63012 | 168820 | GEN-9F  |                             | Human apolipoprotein H mRNA, complete cds                                                | 172  | 163A>T  | M55L  |
| LRPAP1 | M63959 | 104225 | GEN-3EI |                             | Paraoxonase 1 Human alpha-2-macroglobulin receptor-associated protein mRNA, complete cds | 850  | 837G>A  | S     |
| LRPAP1 | M63959 | 104225 | GEN-3EI |                             | Human alpha-2-macroglobulin receptor-associated protein mRNA, complete cds               | 1093 | 1080C>T | 3     |
| LRPAP1 | M63959 | 104225 | GEN-3EI |                             | Human alpha-2-macroglobulin receptor-associated protein mRNA, complete cds               | 1175 | 1162G>A | 3     |
| LRPAP1 | M63959 | 104225 | GEN-3EI |                             | Human alpha-2-macroglobulin receptor-associated protein mRNA, complete cds               | 1249 | 1236C>T | 3     |
| LRPAP1 | M63959 | 104225 | GEN-3EI |                             | Human alpha-2-macroglobulin receptor-associated protein mRNA, complete cds               | 1249 | 1236C>T | 3     |
| LRPAP1 | M63959 | 104225 | GEN-3EI |                             | Human alpha-2-macroglobulin receptor-associated protein mRNA, complete cds               | 1392 | 1379T>G | 3     |

|                                       |        |        |         |                                                     |
|---------------------------------------|--------|--------|---------|-----------------------------------------------------|
| associated protein mRNA, complete cds |        |        |         |                                                     |
| FGFR3                                 | M64347 | 134934 | GEN-3EX | Human novel growth factor receptor mRNA, 3 cds      |
|                                       |        |        |         | 3108C>A 3                                           |
| FGFR3                                 | M64347 | 134934 | GEN-3EX | Human novel growth factor receptor mRNA, 3 cds      |
|                                       |        |        |         | 3715G>A 3                                           |
| M64592                                | M64592 | 120420 | GEN-3X  | Granulocyte colony-stimulating factor               |
|                                       |        |        |         | 271T>G Y91D                                         |
| M64592                                | M64592 | 120420 | GEN-3X  | Granulocyte colony-stimulating factor               |
|                                       |        |        |         | 1533C>T S                                           |
| M64710                                | M64710 | None   | GEN-KUW | Human C-type natriuretic peptide gene, complete cds |
|                                       |        |        |         | 200C>G 3                                            |
| M64710                                | M64710 | None   | GEN-KUW | Human C-type natriuretic peptide gene, complete cds |
|                                       |        |        |         | 778G>A 3                                            |
| M64710                                | M64710 | None   | GEN-KUW | Human C-type natriuretic peptide gene, complete cds |
|                                       |        |        |         | 1216A>G 3                                           |
| M64799                                | M64799 | None   | GEN-4DN | Histamine receptor H2                               |
|                                       |        |        |         | 398T>C V133A                                        |
| M64799                                | M64799 | None   | GEN-4DN | Histamine receptor H2                               |
|                                       |        |        |         | 525A>T K175N                                        |
| M64799                                | M64799 | None   | GEN-4DN | Histamine receptor H2                               |
|                                       |        |        |         | 620A>G K207R                                        |
| M64799                                | M64799 | None   | GEN-4DN | Histamine receptor H2                               |
|                                       |        |        |         | 649A>G N217D                                        |
| M64799                                | M64799 | None   | GEN-4DN | Histamine receptor H2                               |
|                                       |        |        |         | 692A>G K231R                                        |
| M64799                                | M64799 | None   | GEN-4DN | Histamine receptor H2                               |
|                                       |        |        |         | 802G>A V268M                                        |
| M65028                                | M65028 | 602372 | GEN-3FM | Human hnRNP type A/B protein mRNA, complete cds     |
|                                       |        |        |         | 131C>G P44R                                         |
| M65028                                | M65028 | 602372 | GEN-3FM | Human hnRNP type A/B protein mRNA, complete cds     |
|                                       |        |        |         | 453C>G S                                            |
| M65028                                | M65028 | 602372 | GEN-3FM | Human hnRNP type A/B protein mRNA, complete cds     |
|                                       |        |        |         | 1113A>G 3                                           |
| PRKAR1                                | M65066 | 176911 | GEN-    | Human cAMP-dependent                                |
|                                       |        |        |         | 1424C>G 3                                           |

|        |               |         |                                                                                           |      |         |       |
|--------|---------------|---------|-------------------------------------------------------------------------------------------|------|---------|-------|
| B      |               | 3FK     | protein kinase regulatory subunit RI-beta mRNA, 3 end                                     |      |         |       |
| PRKAR1 | M65066 176911 | GEN-3FK | Human cAMP-dependent protein kinase regulatory subunit RI-beta mRNA, 3 end                | 1514 | 1514G>C | 3     |
| PRKAR1 | M65066 176911 | GEN-3FK | Human cAMP-dependent protein kinase regulatory subunit RI-beta mRNA, 3 end                | 1550 | 1550G>C | 3     |
| PRKAR1 | M65066 176911 | GEN-3FK | Human cAMP-dependent protein kinase regulatory subunit RI-beta mRNA, 3 end                | 1862 | 1862G>A | 3     |
| PRKAR1 | M65066 176911 | GEN-3FK | Human cAMP-dependent protein kinase regulatory subunit RI-beta mRNA, 3 end                | 2139 | 2139C>T | 3     |
| C5     | M65134 120900 | GEN-3FT | Human complement component C5 mRNA, 3 end                                                 | 1171 | 1171A>G | I391V |
| EDN2   | M65199 131241 | GEN-CBS | Endothelin 2                                                                              | 384  | 314C>T  | A105V |
| EDN2   | M65199 131241 | GEN-CBS | Endothelin 2                                                                              | 997  | 927A>G  | 3     |
| EDN2   | M65199 131241 | GEN-CBS | Endothelin 2                                                                              | 997  | 927A>G  | 3     |
| M67439 | M67439 126453 | GEN-4EI | Dopamine Receptor D5                                                                      | 1500 | 1353T>A | S     |
| M67439 | M67439 126453 | GEN-4EI | Dopamine Receptor D5                                                                      | 1512 | 1365G>A | F     |
| M67439 | M67439 126453 | GEN-4EI | Dopamine Receptor D5                                                                      | 1566 | 1419G>A | S     |
| M69013 | M69013 139313 | GEN-7L  | Guanine nucleotide binding protein (G protein), alpha 11                                  | 957  | 771C>T  | S     |
| IGFBP6 | M69054 146735 | GEN-3J0 | Human insulin-like growth factor binding protein 6 (IGFBP6) mRNA, complete mature peptide | 751  | 751A>C  | 3     |
| IGFBP6 | M69054 146735 | GEN-3J0 | Human insulin-like growth factor binding protein 6 (IGFBP6) mRNA, complete                | 835  | 835A>C  | 3     |

|        |        |        |             |                                                                                              |      |           |       |
|--------|--------|--------|-------------|----------------------------------------------------------------------------------------------|------|-----------|-------|
| IGFBP6 | M69054 | 146735 | GEN-3J0     | mature peptide<br>Human insulin-like growth factor binding protein 6 (IGFBP6) mRNA, complete | 850  | 850G>A    | 3     |
| M69226 | M69226 | 309850 | GEN-3Z      | mature peptide<br>Monoamine oxidase A                                                        | 435  | 385A>C    | S     |
| M69226 | M69226 | 309850 | GEN-3Z      | Monoamine oxidase A                                                                          | 936  | 886C>T    | F     |
| M69226 | M69226 | 309850 | GEN-3Z      | Monoamine oxidase A                                                                          | 941  | 891T>G    | S     |
| M69226 | M69226 | 309850 | GEN-3Z      | Monoamine oxidase A                                                                          | 941  | 891T>G    | S     |
| M69226 | M69226 | 309850 | GEN-3Z      | Monoamine oxidase A                                                                          | 1076 | 1026A>T   | S     |
| M69226 | M69226 | 309850 | GEN-3Z      | Monoamine oxidase A                                                                          | 1373 | 1323G>A   | F     |
| M69226 | M69226 | 309850 | GEN-3Z      | Monoamine oxidase A                                                                          | 1460 | 1410C>T   | S     |
| M69226 | M69226 | 309850 | GEN-3Z      | Monoamine oxidase A                                                                          | 1460 | 1410C>T   | S     |
| M69226 | M69226 | 309850 | GEN-3Z      | Monoamine oxidase A                                                                          | 1609 | 1559A>G   | K520R |
| SRD5A2 | M74047 | 264600 | GEN-<br>CDC | Human steroid 5-alpha-reductase 2 (SRD5A2) mRNA, complete cds                                | 2379 | 2352A>G   | 3     |
| M74782 | M74782 | 308385 | GEN-64      | Interleukin 3 receptor, alpha (low affinity)                                                 | 1396 | 1250C>T   | 3     |
| M77829 | M77829 | 107776 | GEN-<br>3QJ | Human channel-like integral membrane protein (CHIP28) mRNA, complete cds                     | 172  | 134C>T    | A45V  |
| M77829 | M77829 | 107776 | GEN-<br>3QJ | Human channel-like integral membrane protein (CHIP28) mRNA, complete cds                     | 1249 | 1211C>G   | 3     |
| PAX6   | M77844 | 106210 | GEN-<br>3QG | H.sapiens oculorhombin (aniridia) mRNA, complete cds                                         | 669  | 307C>T    | F     |
| M80646 | M80646 | 274180 | GEN-40      | Thromboxane synthase                                                                         | 756  | 585G>C    | S     |
| M80646 | M80646 | 274180 | GEN-40      | Thromboxane synthase                                                                         | 1240 | 1069C>G   | L357V |
| M81181 | M81181 | 182331 | GEN-G4      | ATPase, Na+/K+ transporting, beta 2 polypeptide                                              | 107  | (-301)C>G | 5     |
| M81181 | M81181 | 182331 | GEN-G4      | ATPase, Na+/K+ transporting, beta 2 polypeptide                                              | 1070 | 663C>A    | S     |
| M81181 | M81181 | 182331 | GEN-G4      | ATPase, Na+/K+ transporting, beta 2 polypeptide                                              | 1974 | 1567C>A   | 3     |

|        |        |        |         |                                                     |         |       |
|--------|--------|--------|---------|-----------------------------------------------------|---------|-------|
| M81181 | M81181 | 182331 | GEN-G4  | transporting, beta 2 polypeptide                    | 1957T>C | 3     |
|        |        |        |         | ATPase, Na+/K+ transporting, beta 2                 |         |       |
| THBS2  | M81339 | 188061 | GEN-3VQ | Human thrombospondin mRNA                           | 1685C>T | 3     |
| THBS2  | M81339 | 188061 | GEN-3VQ | Human thrombospondin mRNA                           | 1921C>T | 3     |
| THBS2  | M81339 | 188061 | GEN-3VQ | Human thrombospondin mRNA                           | 2035T>G | 3     |
| THBS2  | M81339 | 188061 | GEN-3VQ | Human thrombospondin mRNA                           | 2332C>T | 3     |
| THBS2  | M81339 | 188061 | GEN-3VQ | Human thrombospondin mRNA                           | 2562C>T | 3     |
| THBS2  | M81339 | 188061 | GEN-3VQ | Human thrombospondin mRNA                           | 2656C>T | 3     |
| THBS2  | M81339 | 188061 | GEN-3VQ | Human thrombospondin mRNA                           | 2730C>T | 3     |
| M81590 | M81590 | 182131 | GEN-3VZ | Serotonin 5-HT receptors 5-HT1D                     | 129C>T  | S     |
| M81590 | M81590 | 182131 | GEN-3VZ | Serotonin 5-HT receptors 5-HT1D                     | 371T>G  | F124C |
| M81590 | M81590 | 182131 | GEN-3VZ | Serotonin 5-HT receptors 5-HT1D                     | 861G>C  | S     |
| M81590 | M81590 | 182131 | GEN-3VZ | Serotonin 5-HT receptors 5-HT1D                     | 1180G>A | 3     |
| M81757 | M81757 | 603474 | GEN-3W6 | H.sapiens S19 ribosomal protein mRNA, complete cds  | 254A>T  | N85I  |
| M81757 | M81757 | 603474 | GEN-3W6 | H.sapiens S19 ribosomal protein mRNA, complete cds  | 316G>A  | A106T |
| M81757 | M81757 | 603474 | GEN-3W6 | H.sapiens S19 ribosomal protein mRNA, complete cds  | 474G>A  | 3     |
| M81768 | M81768 | 107310 | GEN-G6  | Solute carrier family 9 (sodium/hydrogen exchanger) | 2989G>A | 3     |
| M82962 | M82962 | 600388 | GEN-3XC | Human N-benzoyl-L-tyrosyl-p-amino-benzoic           | 2307T>G | 3     |

|        |        |        |         |                                                                                                                                                                                                                 |         |       |
|--------|--------|--------|---------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------|-------|
| M82962 | M82962 | 600388 | GEN-3XC | acid hydrolase alpha subunit (PPH alpha) mRNA, complete cds<br>Human N-benzoyl-L-tyrosyl-p-amino-benzoic acid hydrolase alpha subunit (PPH alpha) mRNA, complete cds<br>Nicotinic, Cholinergic receptor alpha 5 | 2419A>C | 3     |
| CHRNA5 | M83712 | 118505 | GEN-3YQ | Human 46                                                                                                                                                                                                        | 1192G>A | D398N |
| M84526 | M84526 | 134350 | GEN-3ZL | adipsin/complement factor D mRNA, complete cds<br>Human 399                                                                                                                                                     | (-9)C>T | 5     |
| M84526 | M84526 | 134350 | GEN-3ZL | adipsin/complement factor D mRNA, complete cds<br>Human 408                                                                                                                                                     | 345C>A  | S     |
| M84526 | M84526 | 134350 | GEN-3ZL | adipsin/complement factor D mRNA, complete cds<br>Human 859                                                                                                                                                     | 354A>G  | S     |
| M84526 | M84526 | 134350 | GEN-3ZL | adipsin/complement factor D mRNA, complete cds<br>Human 891                                                                                                                                                     | 805C>T  | 3     |
| M84526 | M84526 | 134350 | GEN-3ZL | adipsin/complement factor D mRNA, complete cds                                                                                                                                                                  | 837G>C  | 3     |
| M84747 | M84747 | 300007 | GEN-45  | Interleukin 9 receptor                                                                                                                                                                                          | 1094G>A | R365H |
| M84755 | M84755 | 162641 | GEN-46  | Neuropeptide Y1                                                                                                                                                                                                 | 1121A>C | K374T |
| TGFBR2 | M85079 | 190182 | GEN-3ZS | Human TGF-beta type II receptor mRNA, complete cds                                                                                                                                                              | 1710A>C | 3     |
| YWHAZ  | M86400 | 601288 | GEN-40Y | Human phospholipase A2 mRNA, complete cds                                                                                                                                                                       | 1569T>A | 3     |
| YWHAZ  | M86400 | 601288 | GEN-40Y | Human phospholipase A2 mRNA, complete cds                                                                                                                                                                       | 2515C>G | 3     |
| YWHAZ  | M86400 | 601288 | GEN-40Y | Human phospholipase A2 mRNA, complete cds                                                                                                                                                                       | 2535A>C | 3     |
| YWHAZ  | M86400 | 601288 | GEN-40Y | Human phospholipase A2 mRNA, complete cds                                                                                                                                                                       | 2572A>C | 3     |
| YWHAZ  | M86400 | 601288 | GEN-40Y | Human phospholipase A2 mRNA, complete cds                                                                                                                                                                       | 2661C>T | 3     |
| YWHAZ  | M86400 | 601288 | GEN-40Y | Human phospholipase A2 mRNA, complete cds                                                                                                                                                                       | 2677A>C | 3     |

|        |        |        |         |     |                                                           |                 |       |
|--------|--------|--------|---------|-----|-----------------------------------------------------------|-----------------|-------|
| GJB2   | M86849 | 121011 | GEN-41L | 40Y | mRNA, complete cds                                        | 1948T>G         | 3     |
|        |        |        |         |     | Human connexin 26 (GJB2) mRNA                             |                 | 1947  |
| GJB2   | M86849 | 121011 | GEN-41L |     | Human connexin 26 (GJB2) mRNA                             | 2036A>G         | 3     |
| OSBP   | M86917 | 167040 | GEN-425 |     | Human oxysterol-binding protein (OSBP) mRNA, complete cds | (-265)T>G       | 5     |
| OSBP   | M86917 | 167040 | GEN-425 |     | Human oxysterol-binding protein (OSBP) mRNA, complete cds | 322C>T          | F     |
| OSBP   | M86917 | 167040 | GEN-425 |     | Human oxysterol-binding protein (OSBP) mRNA, complete cds | 408C>T          | S     |
| OSBP   | M86917 | 167040 | GEN-425 |     | Human oxysterol-binding protein (OSBP) mRNA, complete cds | 454T>G          | S152A |
| M87290 | M87290 | 106165 | GEN-19  |     | Angiotensin receptor AT1                                  | 16T>C           | S6P   |
| M87290 | M87290 | 106165 | GEN-19  |     | Angiotensin receptor AT1                                  | 133G>A          | G45R  |
| M87290 | M87290 | 106165 | GEN-19  |     | Angiotensin receptor AT1                                  | 573T>C          | S     |
| M87290 | M87290 | 106165 | GEN-19  |     | Angiotensin receptor AT1                                  | 573T>C          | S     |
| M87290 | M87290 | 106165 | GEN-19  |     | Angiotensin receptor AT1                                  | 1062A>G         | S     |
| M87290 | M87290 | 106165 | GEN-19  |     | Angiotensin receptor AT1                                  | 1062A>G         | S     |
| M87290 | M87290 | 106165 | GEN-19  |     | Angiotensin receptor AT1                                  | 1150T>G         | 3     |
| M87290 | M87290 | 106165 | GEN-19  |     | Angiotensin receptor AT1                                  | 1166C>A         | 3     |
| M87290 | M87290 | 106165 | GEN-19  |     | Angiotensin receptor AT1                                  | 1166C>A         | 3     |
| M87290 | M87290 | 106165 | GEN-19  |     | Angiotensin receptor AT1                                  | 1166C>A         | 3     |
| M87290 | M87290 | 106165 | GEN-19  |     | Angiotensin receptor AT1                                  | 1173A>G         | 3     |
| M87290 | M87290 | 106165 | GEN-19  |     | Angiotensin receptor AT1                                  | 1397G>A         | 3     |
| M87290 | M87290 | 106165 | GEN-19  |     | Angiotensin receptor AT1                                  | 1517G>T         | 3     |
| M87290 | M87290 | 106165 | GEN-19  |     | Angiotensin receptor AT1                                  | 1605C>T         | 3     |
| M87290 | M87290 | 106165 | GEN-19  |     | Angiotensin receptor AT1                                  | 1636T>C         | 3     |
| M87290 | M87290 | 106165 | GEN-19  |     | Angiotensin receptor AT1                                  | 1878A>G         | 3     |
| M90100 | M90100 | 600262 | GEN-1A  |     | Cyclooxygenase 2 COX2                                     | 2062G>C         | 3     |
| M90100 | M90100 | 600262 | GEN-1A  |     | Cyclooxygenase 2 COX2                                     | 2089-2094ATATTA | 3     |
|        |        |        |         |     |                                                           | >ATATTA         |       |
| M90100 | M90100 | 600262 | GEN-1A  |     | Cyclooxygenase 2 COX2                                     | 2089-           | 3     |



|        |        | 2094delATAT |         | TA                                                 |      |      |                |
|--------|--------|-------------|---------|----------------------------------------------------|------|------|----------------|
| M90100 | M90100 | 600262      | GEN-1A  | Cyclooxygenase 2                                   | COX2 | 2230 | 2133A>G 3      |
| M90100 | M90100 | 600262      | GEN-1A  | Cyclooxygenase 2                                   | COX2 | 2339 | 2242T>C 3      |
| M90100 | M90100 | 600262      | GEN-1A  | Cyclooxygenase 2                                   | COX2 | 2409 | 2312G>A 3      |
| M90100 | M90100 | 600262      | GEN-1A  | Cyclooxygenase 2                                   | COX2 | 2726 | 2629C>T 3      |
| M90100 | M90100 | 600262      | GEN-1A  | Cyclooxygenase 2                                   | COX2 | 2983 | 2886C>T 3      |
| M92269 | M92269 | 114205      | GEN-SV  | Ca Channel alpha1c (alt. splice) L-Type            |      | 3846 | 3846C>T S      |
| M92269 | M92269 | 114205      | GEN-SV  | Ca Channel alpha1c (alt. splice) L-Type            |      | 5505 | 5505G>A S      |
| M92269 | M92269 | 114205      | GEN-SV  | Ca Channel alpha1c (alt. splice) L-Type            |      | 6582 | 6582A>G S      |
| M92269 | M92269 | 114205      | GEN-SV  | Ca Channel alpha1c (alt. splice) L-Type            |      | 6613 | 6613G>C G2205R |
| M92269 | M92269 | 114205      | GEN-SV  | Ca Channel alpha1c (alt. splice) L-Type            |      | 6614 | 6614G>C G2205A |
| PNLIP  | M93285 | 246600      | GEN-48N | Pancreatic lipase (PNLIP)                          |      | 646  | 646G>T V216L   |
| M95678 | M95678 | 604114      | GEN-4A6 | (Dietary supplement) Homo sapiens                  |      | 1346 | 1182T>C S      |
| M95678 | M95678 | 604114      | GEN-4A6 | phospholipase C-beta-2 mRNA, complete cds          |      | 3436 | 3272A>G E1091G |
| M95678 | M95678 | 604114      | GEN-4A6 | phospholipase C-beta-2 mRNA, complete cds          |      | 4137 | 3973C>T 3      |
| M95708 | M95708 | 107271      | GEN-SF  | phospholipase C-beta-2 mRNA, complete cds          |      | 497  | 435C>T 3       |
| M96652 | M96652 | 147851      | GEN-65  | Homo sapiens Interleukin 5 receptor alpha          |      | 883  | 634T>G S212A   |
| GJA4   | M96789 | 121012      | GEN-4B1 | Homo sapiens connexin 37 (GJA4) mRNA, complete cds |      | 211  | 147G>A S       |
| GJA4   | M96789 | 121012      | GEN-4B1 | Homo sapiens connexin 37 (GJA4) mRNA, complete cds |      | 620  | 556G>A V186M   |
| GJA4   | M96789 | 121012      | GEN-4B1 | Homo sapiens connexin 37 (GJA4) mRNA, complete cds |      | 1019 | 955C>T P319S   |

|        |        |        |         |                                                                           |                  |       |
|--------|--------|--------|---------|---------------------------------------------------------------------------|------------------|-------|
| GJA4   | M96789 | 121012 | GEN-4B1 | Homo sapiens connexin 37 (GJA4) mRNA, complete cds                        | 1115A>G          | 3     |
| GJA4   | M96789 | 121012 | GEN-4B1 | Homo sapiens connexin 37 (GJA4) mRNA, complete cds                        | 1159C>A          | 3     |
| GJA4   | M96789 | 121012 | GEN-4B1 | Homo sapiens connexin 37 (GJA4) mRNA, complete cds                        | 1347G>A          | 3     |
| GJA4   | M96789 | 121012 | GEN-4B1 | Homo sapiens connexin 37 (GJA4) mRNA, complete cds                        | 1413C>G          | 3     |
| M98539 | M98539 | 176803 | GEN-SW  | prostaglandin D2 synthase cds                                             | 158C>A           | 3     |
| S70154 | S70154 | 100678 | GEN-GY  | ACAT2 gene                                                                | 632A>G           | K211R |
| S70154 | S70154 | 100678 | GEN-GY  | ACAT2                                                                     | 783T>C           | S     |
| S70154 | S70154 | 100678 | GEN-GY  | ACAT2                                                                     | 783T>C           | S     |
| S70154 | S70154 | 100678 | GEN-GY  | ACAT2                                                                     | 819G>A           | S     |
| S70154 | S70154 | 100678 | GEN-GY  | ACAT2                                                                     | 819G>A           | S     |
| S70154 | S70154 | 100678 | GEN-GY  | ACAT2                                                                     | 1351T>G          | 3     |
| S70154 | S70154 | 100678 | GEN-GY  | ACAT2                                                                     | 1358-1362CTTIA>  | 3     |
| S70154 | S70154 | 100678 | GEN-GY  | ACAT2                                                                     | CTTTA            |       |
| S70154 | S70154 | 100678 | GEN-GY  | ACAT2                                                                     | 1358-1362delCTTT | F     |
| S70154 | S70154 | 100678 | GEN-GY  | ACAT2                                                                     | A                |       |
| S70154 | S70154 | 100678 | GEN-GY  | ACAT2                                                                     | 1382C>A          | 3     |
| S70154 | S70154 | 100678 | GEN-GY  | ACAT2                                                                     | 1382C>A          | 3     |
| ADCYAP | S83513 | 102980 | GEN-3YA | pituitary adenylate cyclase activating polypeptide [human; mRNA, 1940 nt] | 1520G>A          | 3     |
| U00672 | U00672 | 146933 | GEN-4A  | Interleukin 10 receptor                                                   | 3316A>C          | 3     |
| U00672 | U00672 | 146933 | GEN-4A  | Interleukin 10 receptor                                                   | 3463A>G          | 3     |
| U00968 | U00968 | 184756 | GEN-UU  | Human SREBP-1 mRNA, complete cds                                          | 3817G>A          | 3     |
| U02031 | U02031 | 600481 | GEN-WD  | Human sterol regulatory element binding protein-2 mRNA, complete cds      | 972G>A           | S     |

|        |        |        |             |                                                                |      |         |       |
|--------|--------|--------|-------------|----------------------------------------------------------------|------|---------|-------|
| U03642 | U03642 | None   | GEN-<br>KUU | Human G protein-coupled<br>receptor APJ gene,<br>complete cds  | 333  | 135A>C  | S     |
| U03642 | U03642 | None   | GEN-<br>KUU | Human G protein-coupled<br>receptor APJ gene,<br>complete cds  | 1096 | 898G>A  | V300I |
| U03858 | U03858 | 600007 | GEN-<br>MDM | Fms-related tyrosine<br>kinase 3 ligand                        | 683  | 600C>T  | S     |
| U03858 | U03858 | 600007 | GEN-<br>MDM | Fms-related tyrosine<br>kinase 3 ligand                        | 1016 | 933T>C  | 3     |
| U04270 | U04270 | 152427 | GEN-H6      | Potassium channel subunit<br>(h-erg)                           | 1650 | 1467C>T | S     |
| U04270 | U04270 | 152427 | GEN-H6      | Potassium channel subunit<br>(h-erg)                           | 3888 | 3705A>C | 3     |
| HADHA  | U04627 | 600890 | GEN-155     | Human 78 kDa gastrin-<br>binding protein mRNA,<br>complete cds | 1507 | 1507G>A | V503M |
| CDC2L1 | U04815 | 139380 | GEN-<br>15P | Human protein kinase<br>PITSLRE alpha 1 mRNA,<br>complete cds  | 632  | 239C>T  | S80L  |
| CDC2L1 | U04815 | 139380 | GEN-<br>15P | Human protein kinase<br>PITSLRE alpha 1 mRNA,<br>complete cds  | 837  | 444G>C  | S     |
| CDC2L1 | U04815 | 139380 | GEN-<br>15P | Human protein kinase<br>PITSLRE alpha 1 mRNA,<br>complete cds  | 882  | 489C>T  | S     |
| CDC2L1 | U04815 | 139380 | GEN-<br>15P | Human protein kinase<br>PITSLRE alpha 1 mRNA,<br>complete cds  | 945  | 552T>C  | S     |
| CDC2L1 | U04815 | 139380 | GEN-<br>15P | Human protein kinase<br>PITSLRE alpha 1 mRNA,<br>complete cds  | 1119 | 726C>G  | S     |
| CDC2L1 | U04815 | 139380 | GEN-<br>15P | Human protein kinase<br>PITSLRE alpha 1 mRNA,<br>complete cds  | 1131 | 738C>T  | S     |
| CDC2L1 | U04815 | 139380 | GEN-<br>15P | Human protein kinase<br>PITSLRE alpha 1 mRNA,<br>complete cds  | 1134 | 741C>T  | S     |
| CDC2L1 | U04815 | 139380 | GEN-<br>15P | Human protein kinase<br>PITSLRE alpha 1 mRNA,<br>complete cds  | 1193 | 800T>A  | L267Q |

|        |        |        |         |                                                               |      |         |       |
|--------|--------|--------|---------|---------------------------------------------------------------|------|---------|-------|
| CDC2L1 | U04815 | 139380 | GEN-15P | Human protein kinase<br>PITSLRE alpha 1 mRNA,<br>complete cds | 1266 | 873T>C  | S     |
| CDC2L1 | U04815 | 139380 | GEN-15P | Human protein kinase<br>PITSLRE alpha 1 mRNA,<br>complete cds | 1314 | 921G>T  | K307N |
| CDC2L1 | U04815 | 139380 | GEN-15P | Human protein kinase<br>PITSLRE alpha 1 mRNA,<br>complete cds | 1692 | 1299C>A | D433E |
| CDC2L1 | U04815 | 139380 | GEN-15P | Human protein kinase<br>PITSLRE alpha 1 mRNA,<br>complete cds | 1700 | 1307T>A | L436Q |
| CDC2L1 | U04815 | 139380 | GEN-15P | Human protein kinase<br>PITSLRE alpha 1 mRNA,<br>complete cds | 1706 | 1313A>G | E438G |
| CDC2L1 | U04815 | 139380 | GEN-15P | Human protein kinase<br>PITSLRE alpha 1 mRNA,<br>complete cds | 1776 | 1383C>T | S     |
| DDH1   | U05598 | 600450 | GEN-184 | Human dihydrodiol<br>dehydrogenase mRNA,<br>complete cds      | 38   | 15C>T   | S     |
| DDH1   | U05598 | 600450 | GEN-184 | Human dihydrodiol<br>dehydrogenase mRNA,<br>complete cds      | 282  | 259A>T  | S87C  |
| DDH1   | U05598 | 600450 | GEN-184 | Human dihydrodiol<br>dehydrogenase mRNA,<br>complete cds      | 350  | 327C>T  | S     |
| DDH1   | U05598 | 600450 | GEN-184 | Human dihydrodiol<br>dehydrogenase mRNA,<br>complete cds      | 365  | 342T>C  | S     |
| DDH1   | U05598 | 600450 | GEN-184 | Human dihydrodiol<br>dehydrogenase mRNA,<br>complete cds      | 464  | 441G>A  | S     |
| DDH1   | U05598 | 600450 | GEN-184 | Human dihydrodiol<br>dehydrogenase mRNA,<br>complete cds      | 474  | 451A>G  | M151V |
| DDH1   | U05598 | 600450 | GEN-184 | Human dihydrodiol<br>dehydrogenase mRNA,<br>complete cds      | 532  | 509A>G  | H170R |
| DDH1   | U05598 | 600450 | GEN-184 | Human dihydrodiol<br>dehydrogenase mRNA,<br>complete cds      | 538  | 515T>A  | L172Q |

|         |        |        |         |                                                                                               |      |         |       |
|---------|--------|--------|---------|-----------------------------------------------------------------------------------------------|------|---------|-------|
| DDH1    | U05598 | 600450 | GEN-184 | complete cds<br>Human dihydrodiol<br>dehydrogenase mRNA,                                      | 689  | 666T>C  | S     |
| DDH1    | U05598 | 600450 | GEN-184 | complete cds<br>Human dihydrodiol<br>dehydrogenase mRNA,                                      | 806  | 783G>A  | S     |
| DDH1    | U05598 | 600450 | GEN-184 | complete cds<br>Human dihydrodiol<br>dehydrogenase mRNA,                                      | 872  | 849G>T  | S     |
| DDH1    | U05598 | 600450 | GEN-184 | complete cds<br>Human dihydrodiol<br>dehydrogenase mRNA,                                      | 952  | 929T>G  | I310S |
| DDH1    | U05598 | 600450 | GEN-184 | complete cds<br>Human dihydrodiol<br>dehydrogenase mRNA,                                      | 1020 | 997G>A  | 3     |
| DDH1    | U05598 | 600450 | GEN-184 | complete cds<br>Human dihydrodiol<br>dehydrogenase mRNA,                                      | 1035 | 1012G>A | 3     |
| DDH1    | U05598 | 600450 | GEN-184 | complete cds<br>Human dihydrodiol<br>dehydrogenase mRNA,                                      | 1112 | 1089C>T | 3     |
| HSD17B3 | U05659 | 264300 | GEN-186 | complete cds<br>Human 17beta-<br>hydroxysteroid<br>dehydrogenase type 3<br>mRNA, complete cds | 894  | 846G>C  | S     |
| U07225  | U07225 | 600041 | GEN-1DM | P2Y2 purinoceptor                                                                             | 2008 | 1763G>A | 3     |
| U09117  | U09117 | 602142 | GEN-1GC | Phospholipase C delta-1                                                                       | 333  | 239G>A  | R80H  |
| U09117  | U09117 | 602142 | GEN-1GC | Phospholipase C delta-1                                                                       | 460  | 366G>A  | S     |
| U09117  | U09117 | 602142 | GEN-1GC | Phospholipase C delta-1                                                                       | 1858 | 1764G>A | S     |
| SLC18A3 | U09210 | 600336 | GEN-4F3 | Human vesicular<br>acetylcholine transporter<br>mRNA, complete cds                            | 838  | 396T>C  | S     |
| SLC18A3 | U09210 | 600336 | GEN-4F3 | Human vesicular<br>acetylcholine transporter<br>mRNA, complete cds                            | 1369 | 927A>G  | S     |
| SLC18A3 | U09210 | 600336 | GEN-    | Human vesicular                                                                               | 1567 | 1125C>G | S     |

|         |        |        |         |         |                                                              |         |       |
|---------|--------|--------|---------|---------|--------------------------------------------------------------|---------|-------|
| SLC18A3 | U09210 | 600336 | GEN-4F3 | 4F3     | acetylcholine transporter mRNA, complete cds                 | 1638G>T | 3     |
| SLC18A3 | U09210 | 600336 | GEN-4F3 | 4F3     | Human vesicular acetylcholine transporter mRNA, complete cds | 1757G>A | 3     |
| SLC18A3 | U09210 | 600336 | GEN-4F3 | 4F3     | Human vesicular acetylcholine transporter mRNA, complete cds | 1907G>T | 3     |
| U09648  | U09648 | 600650 | GEN-1I  | GEN-1I  | Human vesicular acetylcholine transporter mRNA, complete cds | 2040G>A | 3     |
| U09648  | U09648 | 600650 | GEN-1I  | GEN-1I  | Carnitine                                                    | 2159G>A | 3     |
| U09648  | U09648 | 600650 | GEN-1I  | GEN-1I  | Palmitoyltransferase II                                      | 2276G>A | 3     |
| U09648  | U09648 | 600650 | GEN-1I  | GEN-1I  | Palmitoyltransferase II                                      | 2309G>A | 3     |
| U09759  | U09759 | 602896 | GEN-1HA | GEN-1HA | Palmitoyltransferase II                                      | 152A>G  | N51S  |
| U09759  | U09759 | 602896 | GEN-1HA | GEN-1HA | Human protein kinase (JNK2) mRNA, complete cds               | 928A>G  | I310V |
| U09759  | U09759 | 602896 | GEN-1HA | GEN-1HA | Human protein kinase (JNK2) mRNA, complete cds               | 1129C>T | P377S |
| U09759  | U09759 | 602896 | GEN-1HA | GEN-1HA | Human protein kinase (JNK2) mRNA, complete cds               | 1408C>T | 3     |
| U09806  | U09806 | None   | GEN-4FZ | GEN-4FZ | Human protein kinase (JNK2) mRNA, complete cds               | 120T>C  | S     |
| U09806  | U09806 | None   | GEN-4FZ | GEN-4FZ | Human protein kinase (JNK2) mRNA, complete cds               | 473G>A  | R158Q |
| U09806  | U09806 | None   | GEN-4FZ | GEN-4FZ | Human protein kinase (JNK2) mRNA, complete cds               | 550C>T  | F     |

|        |        |        |         |                                                                                                   |         |       |
|--------|--------|--------|---------|---------------------------------------------------------------------------------------------------|---------|-------|
| U09806 | U09806 | None   | GEN-4FZ | reductase mRNA, partial cds<br>Human 668<br>methylenetetrahydrofolate reductase mRNA, partial cds | 668C>T  | A223V |
| U09806 | U09806 | None   | GEN-4FZ | Human 1059<br>methylenetetrahydrofolate reductase mRNA, partial cds                               | 1059T>C | S     |
| U09806 | U09806 | None   | GEN-4FZ | Human 1289<br>methylenetetrahydrofolate reductase mRNA, partial cds                               | 1289C>A | E430A |
| U09806 | U09806 | None   | GEN-4FZ | Human 1308<br>methylenetetrahydrofolate reductase mRNA, partial cds                               | 1308T>C | 3     |
| THPO   | U11025 | 600044 | GEN-1JW | Human megakaryocyte 76<br>growth and development factor (MGDF) mRNA, complete cds                 | 41T>C   | L14P  |
| THPO   | U11025 | 600044 | GEN-1JW | Human megakaryocyte 172<br>growth and development factor (MGDF) mRNA, complete cds                | 137G>A  | R46K  |
| THPO   | U11025 | 600044 | GEN-1JW | Human megakaryocyte 382<br>growth and development factor (MGDF) mRNA, complete cds                | 347G>A  | G116E |
| THPO   | U11025 | 600044 | GEN-1JW | Human megakaryocyte 674<br>growth and development factor (MGDF) mRNA, complete cds                | 639T>A  | S     |
| THPO   | U11025 | 600044 | GEN-1JW | Human megakaryocyte 1132<br>growth and development factor (MGDF) mRNA, complete cds               | 1097G>A | 3     |
| U12507 | U12507 | 600681 | GEN-1MD | Cardiac inward rectifier potassium channel (HH-IRK1)                                              | 13C>A   | S     |

|        |        |        |         |                                                                               |      |          |       |
|--------|--------|--------|---------|-------------------------------------------------------------------------------|------|----------|-------|
| U12507 | U12507 | 600681 | GEN-1MD | Cardiac inward rectifier potassium channel (HHRK1)                            | 1597 | 1272G>A  | S     |
| U12789 | U12789 | 600234 | GEN-4F  | HMG CoA synthase (HSH1) mitochondrial                                         | 720  | 720T>A   | H240Q |
| U13737 | U13737 | 600636 | GEN-1PC | Human cysteine protease CPP32 isoform alpha mRNA, complete cds                | 2356 | 2132A>C  | 3     |
| U13737 | U13737 | 600636 | GEN-1PC | Human cysteine protease CPP32 isoform alpha mRNA, complete cds                | 2535 | 2311C>T  | 3     |
| CTGF   | U14750 | 121009 | GEN-1S3 | Human connective tissue growth factor mRNA, partial cds                       | 1878 | 1878A>C  | 3     |
| U16660 | U16660 | 600696 | GEN-1YD | Human peroxisomal enoyl-CoA hydratase-like protein (HPXEL) mRNA, complete cds | 149  | 122A>C   | E41A  |
| U16660 | U16660 | 600696 | GEN-1YD | Human peroxisomal enoyl-CoA hydratase-like protein (HPXEL) mRNA, complete cds | 402  | 375G>A   | S     |
| U16660 | U16660 | 600696 | GEN-1YD | Human peroxisomal enoyl-CoA hydratase-like protein (HPXEL) mRNA, complete cds | 802  | 775C>G   | P259A |
| U16660 | U16660 | 600696 | GEN-1YD | Human peroxisomal enoyl-CoA hydratase-like protein (HPXEL) mRNA, complete cds | 1157 | 1130G>A  | 3     |
| U16957 | U16957 | 300034 | GEN-1L  | Angiotensin receptor AT2                                                      | 263  | 123T>C   | S     |
| U16957 | U16957 | 300034 | GEN-1L  | Angiotensin receptor AT2                                                      | 883  | 743G>A   | R248K |
| STAR   | U17280 | 600617 | GEN-208 | Human steroidogenic acute regulatory protein (STAR) mRNA, complete cds        | 1439 | 1313C>T  | 3     |
| NOS1   | U17327 | 163731 | GEN-209 | Human neuronal nitric oxide synthase (NOS1) mRNA, complete cds                | 3391 | 2706C>T  | S     |
| U19487 | U19487 | 176804 | GEN-4I  | PROSTAGLANDIN E2 RECEPTOR, EP2                                                | 85   | (-72)A>G | 5     |



|        |        |        |         |                                                                      |      |         |       |
|--------|--------|--------|---------|----------------------------------------------------------------------|------|---------|-------|
| U19487 | U19487 | 176804 | GEN-4I  | PROSTAGLANDIN E2 RECEPTOR, EP2 SUBTYPE                               | 231  | 75A>T   | S     |
| U19775 | U19775 | 600289 | GEN-22C | Human MAP kinase Mxi2 (MXI2) mRNA, complete cds                      | 731  | 688G>A  | D230N |
| U20157 | U20157 | 601690 | GEN-234 | Human platelet-activating factor acetylhydrolase mRNA, complete cds  | 1297 | 1136T>C | V379A |
| U20180 | U20180 | 147582 | GEN-236 | Human iron-regulatory protein 2 (IRP2) mRNA, partial cds             | 2583 | 2583C>T | S     |
| U20536 | U20536 | 601532 | GEN-23K | Human cysteine protease Mch2 isoform alpha (Mch2) mRNA, complete cds | 982  | 904C>T  | 3     |
| U20536 | U20536 | 601532 | GEN-23K | Human cysteine protease Mch2 isoform alpha (Mch2) mRNA, complete cds | 1117 | 1039G>A | 3     |
| U20536 | U20536 | 601532 | GEN-23K | Human cysteine protease Mch2 isoform alpha (Mch2) mRNA, complete cds | 1322 | 1244T>C | 3     |
| U20536 | U20536 | 601532 | GEN-23K | Human cysteine protease Mch2 isoform alpha (Mch2) mRNA, complete cds | 1363 | 1285T>C | 3     |
| U27325 | U27325 | 188070 | GEN-7N  | Thromboxane A2 TP receptor, platelet and non-platelet                | 302  | 179G>T  | R60L  |
| U27325 | U27325 | 188070 | GEN-7N  | Thromboxane A2 TP receptor, platelet and non-platelet                | 918  | 795T>C  | S     |
| U27467 | U27467 | 601056 | GEN-2BX | Human Bcl-2 related (Bfl-1) mRNA, complete cds                       | 476  | 442T>C  | F148L |
| U27467 | U27467 | 601056 | GEN-2BX | Human Bcl-2 related (Bfl-1) mRNA, complete cds                       | 481  | 447A>G  | S     |
| U27467 | U27467 | 601056 | GEN-2BX | Human Bcl-2 related (Bfl-1) mRNA, complete cds                       | 542  | 508C>G  | L170V |
| U27467 | U27467 | 601056 | GEN-2BX | Human Bcl-2 related (Bfl-1) mRNA, complete cds                       | 578  | 544C>T  | 3     |
| U27467 | U27467 | 601056 | GEN-2BX | Human Bcl-2 related (Bfl-1) mRNA, complete cds                       | 614  | 580T>C  | 3     |

|        |        |        |         |                                                               |      |                 |       |
|--------|--------|--------|---------|---------------------------------------------------------------|------|-----------------|-------|
| U27467 | U27467 | 601056 | GEN-2BX | Human Bcl-2 related (Bfl-1) mRNA, complete cds                | 616  | 582G>A          | 3     |
| U31628 | U31628 | 601070 | GEN-4J  | Interleukin 15 receptor alpha chain                           | 1250 | 1168G>T         | 3     |
| U32324 | U32324 | 600939 | GEN-4K  | interleukin 11 receptor alpha chain                           | 1266 | 1205C>A         | P402Q |
| U32324 | U32324 | 600939 | GEN-4K  | interleukin 11 receptor alpha chain                           | 1513 | 1452C>T         | 3     |
| U32500 | U32500 | 162642 | GEN-1P  | Neuropeptide Y2                                               | 407  | 159C>T          | S     |
| U32500 | U32500 | 162642 | GEN-1P  | Neuropeptide Y2                                               | 833  | 585T>C          | S     |
| U32500 | U32500 | 162642 | GEN-1P  | Neuropeptide Y2                                               | 833  | 585T>C          | S     |
| U32500 | U32500 | 162642 | GEN-1P  | Neuropeptide Y2                                               | 1184 | 936T>C          | S     |
| U32500 | U32500 | 162642 | GEN-1P  | Neuropeptide Y2                                               | 1184 | 936T>C          | S     |
| U32500 | U32500 | 162642 | GEN-1P  | Neuropeptide Y2                                               | 1706 | 1458-1460TAT>TA | 3     |
| U32500 | U32500 | 162642 | GEN-1P  | Neuropeptide Y2                                               | 1706 | 1458-1460delTAT | 3     |
| U32500 | U32500 | 162642 | GEN-1P  | Neuropeptide Y2                                               | 2782 | 2534^2535ins CA | F     |
| U32989 | U32989 | 191070 | GEN-2JH | Human tryptophan oxygenase (TDO) mRNA, complete cds           | 991  | 927G>A          | S     |
| U33052 | U33052 | 602549 | GEN-2JL | Human lipid-activated, protein kinase PRK2 mRNA, complete cds | 34   | 25G>C           | E9Q   |
| U33052 | U33052 | 602549 | GEN-2JL | Human lipid-activated, protein kinase PRK2 mRNA, complete cds | 430  | 421T>C          | S     |
| U33052 | U33052 | 602549 | GEN-2JL | Human lipid-activated, protein kinase PRK2 mRNA, complete cds | 1112 | 1103T>G         | F368C |
| GSS    | U34683 | 601002 | GEN-2LF | Human glutathione synthetase mRNA, complete cds               | 364  | 324G>A          | S     |
| FGF8   | U36223 | 600483 | GEN-2MX | Human fibroblast growth factor 8 (FGF-8) mRNA, complete cds   | 300  | 291T>C          | S     |
| FGF8   | U36223 | 600483 | GEN-2MX | Human fibroblast growth factor 8 (FGF-8) mRNA, complete cds   | 645  | 636G>C          | S     |

|        |        |        |         |                                                                                               |      |         |        |
|--------|--------|--------|---------|-----------------------------------------------------------------------------------------------|------|---------|--------|
| FGF8   | U36223 | 600483 | GEN-2MX | Human fibroblast growth factor 8 (FGF-8) mRNA, complete cds                                   | 648  | 639A>G  | S      |
| U37448 | U37448 | 601761 | GEN-2OC | Human Mch3 isoform alpha (Mch3) mRNA, complete cds                                            | 736  | 693G>A  | S      |
| U37448 | U37448 | 601761 | GEN-2OC | Human Mch3 isoform alpha (Mch3) mRNA, complete cds                                            | 1285 | 1242T>C | 3      |
| U37448 | U37448 | 601761 | GEN-2OC | Human Mch3 isoform alpha (Mch3) mRNA, complete cds                                            | 1294 | 1251T>C | 3      |
| U37448 | U37448 | 601761 | GEN-2OC | Human Mch3 isoform alpha (Mch3) mRNA, complete cds                                            | 1580 | 1537A>T | 3      |
| U37448 | U37448 | 601761 | GEN-2OC | Human Mch3 isoform alpha (Mch3) mRNA, complete cds                                            | 1621 | 1578G>T | 3      |
| U37448 | U37448 | 601761 | GEN-2OC | Human Mch3 isoform alpha (Mch3) mRNA, complete cds                                            | 1715 | 1672G>A | 3      |
| U37448 | U37448 | 601761 | GEN-2OC | Human Mch3 isoform alpha (Mch3) mRNA, complete cds                                            | 1764 | 1721G>A | 3      |
| U38545 | U38545 | 602382 | GEN-2PB | Human ARF-activated phosphatidylcholine-specific phospholipase D1a (hPLD1) mRNA, complete cds | 3100 | 3005T>G | F1002C |
| U40002 | U40002 | 151750 | GEN-2RH | Human hormone-sensitive lipase testicular isoform mRNA, complete cds                          | 2076 | 1799C>A | P600H  |
| U40038 | U40038 | 600998 | GEN-70  | Guanine nucleotide binding protein (G protein), q polypeptide                                 | 825  | 783C>T  | S      |
| U40038 | U40038 | 600998 | GEN-70  | Guanine nucleotide binding protein (G protein), q polypeptide                                 | 878  | 836T>C  | L279P  |
| U40038 | U40038 | 600998 | GEN-70  | Guanine nucleotide binding protein (G protein), q polypeptide                                 | 1029 | 987G>A  | S      |

|        |        |        |             |                                                                     |      |         |       |
|--------|--------|--------|-------------|---------------------------------------------------------------------|------|---------|-------|
| U40038 | U40038 | 600998 | GEN-70      | polypeptide<br>Guanine nucleotide binding<br>protein (G protein), q | 1051 | 1009A>G | I337V |
| U40038 | U40038 | 600998 | GEN-70      | polypeptide<br>Guanine nucleotide binding<br>protein (G protein), q | 1068 | 1026T>A | S     |
| U40038 | U40038 | 600998 | GEN-70      | polypeptide<br>Guanine nucleotide binding<br>protein (G protein), q | 1093 | 1051T>C | S     |
| U40347 | U40347 | 600950 | GEN-<br>2RK | Human serotonin N-<br>acetyltransferase mRNA,<br>complete cds       | 382  | 148G>A  | E50K  |
| U40396 | U40396 | 602691 | GEN-6W      | Steroid receptor<br>coactivator (SRC-1)                             | 285  | 229A>C  | K77Q  |
| U40396 | U40396 | 602691 | GEN-6W      | Steroid receptor<br>coactivator (SRC-1)                             | 314  | 258A>T  | K86N  |
| U40396 | U40396 | 602691 | GEN-6W      | Steroid receptor<br>coactivator (SRC-1)                             | 336  | 280C>T  | P94S  |
| U40396 | U40396 | 602691 | GEN-6W      | Steroid receptor<br>coactivator (SRC-1)                             | 688  | 632C>T  | T211I |
| U40396 | U40396 | 602691 | GEN-6W      | Steroid receptor<br>coactivator (SRC-1)                             | 970  | 914C>A  | A305E |
| U40396 | U40396 | 602691 | GEN-6W      | Steroid receptor<br>coactivator (SRC-1)                             | 1511 | 1455G>A | S     |
| U40396 | U40396 | 602691 | GEN-6W      | Steroid receptor<br>coactivator (SRC-1)                             | 2377 | 2321C>T | T774M |
| U40396 | U40396 | 602691 | GEN-6W      | Steroid receptor<br>coactivator (SRC-1)                             | 2730 | 2674C>T | P892S |
| U40583 | U40583 | 118511 | GEN-4O      | Nicotinic, Cholinergic<br>receptor alpha 7                          | 661  | 654T>C  | S     |
| U40583 | U40583 | 118511 | GEN-4O      | Nicotinic, Cholinergic<br>receptor alpha 7                          | 697  | 690A>G  | S     |
| U40583 | U40583 | 118511 | GEN-4O      | Nicotinic, Cholinergic<br>receptor alpha 7                          | 940  | 933G>A  | S     |
| U40583 | U40583 | 118511 | GEN-4O      | Nicotinic, Cholinergic<br>receptor alpha 7                          | 1276 | 1269T>C | S     |
| U40583 | U40583 | 118511 | GEN-4O      | Nicotinic, Cholinergic<br>receptor alpha 7                          | 1790 | 1783A>T | 3     |
| U40583 | U40583 | 118511 | GEN-4O      | Nicotinic, Cholinergic<br>receptor alpha 7                          | 1792 | 1785T>A | 3     |

|        |        |        |         |                                                                                 |      |         |       |
|--------|--------|--------|---------|---------------------------------------------------------------------------------|------|---------|-------|
| U43142 | U43142 | 601528 | GEN-2UM | Human vascular endothelial growth factor related protein VRP mRNA, complete cds | 1499 | 1128C>T | S     |
| U45448 | U45448 | 600845 | GEN-4FI | Human P2x1 receptor mRNA, complete cds                                          | 1424 | 1228A>G | 3     |
| U45448 | U45448 | 600845 | GEN-4FI | Human P2x1 receptor mRNA, complete cds                                          | 1604 | 1408C>G | 3     |
| U45448 | U45448 | 600845 | GEN-4FI | Human P2x1 receptor mRNA, complete cds                                          | 1719 | 1523G>A | 3     |
| U45448 | U45448 | 600845 | GEN-4FI | Human P2x1 receptor mRNA, complete cds                                          | 1827 | 1631G>A | 3     |
| U45448 | U45448 | 600845 | GEN-4FI | Human P2x1 receptor mRNA, complete cds                                          | 2286 | 2090G>A | 3     |
| U48730 | U48730 | 601511 | GEN-JA  | Transcription Factor Stat5b                                                     | 494  | 484T>C  | S     |
| U48730 | U48730 | 601511 | GEN-JA  | Transcription Factor Stat5b                                                     | 496  | 486A>G  | S     |
| U48730 | U48730 | 601511 | GEN-JA  | Transcription Factor Stat5b                                                     | 499  | 489A>G  | S     |
| U48730 | U48730 | 601511 | GEN-JA  | Transcription Factor Stat5b                                                     | 502  | 492G>A  | S     |
| U48730 | U48730 | 601511 | GEN-JA  | Transcription Factor Stat5b                                                     | 570  | 560G>C  | G187A |
| U48730 | U48730 | 601511 | GEN-JA  | Transcription Factor Stat5b                                                     | 573  | 563C>A  | P188Q |
| U48730 | U48730 | 601511 | GEN-JA  | Transcription Factor Stat5b                                                     | 1003 | 993G>A  | S     |
| U48730 | U48730 | 601511 | GEN-JA  | Transcription Factor Stat5b                                                     | 1063 | 1053T>C | S     |
| U48730 | U48730 | 601511 | GEN-JA  | Transcription Factor Stat5b                                                     | 1066 | 1056G>A | S     |
| U48730 | U48730 | 601511 | GEN-JA  | Transcription Factor Stat5b                                                     | 1105 | 1095C>T | S     |
| U48730 | U48730 | 601511 | GEN-JA  | Transcription Factor Stat5b                                                     | 1159 | 1149C>T | S     |
| U48730 | U48730 | 601511 | GEN-JA  | Transcription Factor Stat5b                                                     | 1969 | 1959C>T | S     |
| U49516 | U49516 | 312861 | GEN-1Q  | Serotonin 5-HT receptors 5-HT2C                                                 | 2915 | 2187A>C | 3     |
| U49516 | U49516 | 312861 | GEN-1Q  | Serotonin 5-HT receptors 5-HT2C                                                 | 2947 | 2219A>G | 3     |
| U50929 | U50929 | 602888 | GEN-JF  | Methionine synthetase (aka homocysteine methyltransferase)                      | 2017 | 1991A>G | 3     |
| U50929 | U50929 | 602888 | GEN-JF  | Methionine synthetase (aka homocysteine methyltransferase)                      | 2418 | 2392A>T | 3     |
| U51478 | U51478 | 601867 | GEN-31Z | Human sodium/potassium-transporting ATPase beta-3 subunit mRNA, complete        | 1099 | 1071G>C | 3     |

|        |        |        |         |                                                                              |      |         |      |
|--------|--------|--------|---------|------------------------------------------------------------------------------|------|---------|------|
| U51478 | U51478 | 601867 | GEN-31Z | Human sodium/potassium-transporting ATPase beta-3 subunit mRNA, complete cds | 1121 | 1093T>C | 3    |
| U51478 | U51478 | 601867 | GEN-31Z | Human sodium/potassium-transporting ATPase beta-3 subunit mRNA, complete cds | 1133 | 1105G>T | 3    |
| U56390 | U56390 | 602234 | GEN-36X | Human cysteine protease ICE-LAP6 mRNA, complete cds                          | 411  | 408C>T  | S    |
| U56976 | U56976 | 171891 | GEN-379 | Human calmodulin dependent phosphodiesterase PDE1B1 mRNA, complete cds       | 1510 | 1476C>T | S    |
| DES    | U59167 | 125660 | GEN-39F | Human desmin mRNA, complete cds                                              | 140  | 60C>G   | S    |
| DES    | U59167 | 125660 | GEN-39F | Human desmin mRNA, complete cds                                              | 905  | 825T>C  | S    |
| DES    | U59167 | 125660 | GEN-39F | Human desmin mRNA, complete cds                                              | 1091 | 1011C>G | S    |
| DES    | U59167 | 125660 | GEN-39F | Human desmin mRNA, complete cds                                              | 1181 | 1101G>A | S    |
| DES    | U59167 | 125660 | GEN-39F | Human desmin mRNA, complete cds                                              | 2176 | 2096C>A | 3    |
| U60519 | U60519 | 601762 | GEN-3AZ | Human apoptotic cysteine protease Mch4 (Mch4) mRNA, complete cds             | 304  | 157G>A  | E53K |
| U60519 | U60519 | 601762 | GEN-3AZ | Human apoptotic cysteine protease Mch4 (Mch4) mRNA, complete cds             | 324  | 177A>G  | S    |
| CHRNA2 | U62431 | 118502 | GEN-4EN | Nicotinic, Cholinergic receptor alpha 2                                      | 2296 | 1742C>G | 3    |
| CHRNA2 | U62431 | 118502 | GEN-4EN | Nicotinic, Cholinergic receptor alpha 2                                      | 2387 | 1833C>T | 3    |
| CHRNA2 | U62431 | 118502 | GEN-4EN | Nicotinic, Cholinergic receptor alpha 2                                      | 2504 | 1950G>T | 3    |
| CHRNA2 | U62431 | 118502 | GEN-4EN | Nicotinic, Cholinergic receptor alpha 2                                      | 2538 | 1984G>A | 3    |

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|--------|--------|--------|-------------|-------------------------------------------------------------|------|---------|--------|
| U62433 | U62433 | 118504 | GEN-4P      | Nicotinic, Cholinergic<br>receptor alpha 4                  | 870  | 639C>T  | S      |
| U62433 | U62433 | 118504 | GEN-4P      | Nicotinic, Cholinergic<br>receptor alpha 4                  | 870  | 639C>T  | S      |
| U62433 | U62433 | 118504 | GEN-4P      | Nicotinic, Cholinergic<br>receptor alpha 4                  | 909  | 678C>T  | S      |
| U62433 | U62433 | 118504 | GEN-4P      | Nicotinic, Cholinergic<br>receptor alpha 4                  | 909  | 678C>T  | S      |
| U62433 | U62433 | 118504 | GEN-4P      | Nicotinic, Cholinergic<br>receptor alpha 4                  | 1440 | 1209T>G | S      |
| U62433 | U62433 | 118504 | GEN-4P      | Nicotinic, Cholinergic<br>receptor alpha 4                  | 1440 | 1209T>G | S      |
| U62433 | U62433 | 118504 | GEN-4P      | Nicotinic, Cholinergic<br>receptor alpha 4                  | 1458 | 1227C>T | S      |
| U62433 | U62433 | 118504 | GEN-4P      | Nicotinic, Cholinergic<br>receptor alpha 4                  | 1584 | 1353G>A | S      |
| U62433 | U62433 | 118504 | GEN-4P      | Nicotinic, Cholinergic<br>receptor alpha 4                  | 1781 | 1550C>T | S517L  |
| U62433 | U62433 | 118504 | GEN-4P      | Nicotinic, Cholinergic<br>receptor alpha 4                  | 1860 | 1629C>T | S      |
| U62433 | U62433 | 118504 | GEN-4P      | Nicotinic, Cholinergic<br>receptor alpha 4                  | 1860 | 1629C>T | S      |
| U62433 | U62433 | 118504 | GEN-4P      | Nicotinic, Cholinergic<br>receptor alpha 4                  | 1890 | 1659G>A | S      |
| U62433 | U62433 | 118504 | GEN-4P      | Nicotinic, Cholinergic<br>receptor alpha 4                  | 1890 | 1659G>A | S      |
| U62768 | U62768 | 151300 | GEN-<br>3CR | Human oxytocinase splice<br>variant 1 mRNA, complete<br>cds | 3356 | 3295G>C | 3      |
| U62768 | U62768 | 151300 | GEN-<br>3CR | Human oxytocinase splice<br>variant 1 mRNA, complete<br>cds | 3547 | 3486C>T | 3      |
| U70136 | U70136 | 600044 | GEN-4R      | Thrombopoietin                                              | 4138 | 4105G>T | A1369S |
| U70136 | U70136 | 600044 | GEN-4R      | Thrombopoietin                                              | 4141 | 4108T>A | F1370I |
| U70867 | U70867 | 601460 | GEN-4S      | prostaglandin transporter<br>hPGT                           | 2706 | 2615T>G | 3      |
| U70867 | U70867 | 601460 | GEN-4S      | prostaglandin transporter<br>hPGT                           | 2839 | 2748T>A | 3      |
| U70867 | U70867 | 601460 | GEN-4S      | prostaglandin transporter<br>hPGT                           | 2908 | 2817A>G | 3      |
| U70867 | U70867 | 601460 | GEN-4S      | prostaglandin transporter<br>hPGT                           | 3171 | 3080A>G | 3      |

|        |        |        |         |                                                                                            |      |         |       |
|--------|--------|--------|---------|--------------------------------------------------------------------------------------------|------|---------|-------|
| U70867 | U70867 | 601460 | GEN-4S  | prostaglandin transporter<br>hPGT                                                          | 3171 | 3080A>G | 3     |
| U70867 | U70867 | 601460 | GEN-4S  | prostaglandin transporter<br>hPGT                                                          | 3253 | 3162A>G | 3     |
| U70867 | U70867 | 601460 | GEN-4S  | prostaglandin transporter<br>hPGT                                                          | 3255 | 3164A>G | 3     |
| U70867 | U70867 | 601460 | GEN-4S  | prostaglandin transporter<br>hPGT                                                          | 3594 | 3503T>A | 3     |
| U71321 | U71321 | 602623 | GEN-2TW | Human FK506-binding<br>protein FKBP51 mRNA,<br>complete cds                                | 1248 | 1095C>T | S     |
| U71321 | U71321 | 602623 | GEN-2TW | Human FK506-binding<br>protein FKBP51 mRNA,<br>complete cds                                | 1425 | 1272G>A | S     |
| U73338 | U73338 | 156570 | GEN-69  | Methionine Synthase                                                                        | 1158 | 764G>A  | C255Y |
| U73338 | U73338 | 156570 | GEN-69  | Methionine Synthase                                                                        | 5095 | 4701G>A | 3     |
| U73338 | U73338 | 156570 | GEN-69  | Methionine Synthase                                                                        | 6750 | 6356G>A | 3     |
| U78294 | U78294 | 603697 | GEN-3QZ | Homo sapiens 15S-<br>lipoxigenase mRNA,<br>complete cds                                    | 2449 | 2378A>G | 3     |
| U79269 | U79269 | 123829 | GEN-K7  | Cyclin-Dependent Protein<br>Kinase                                                         | 1281 | 972A>T  | 3     |
| U81375 | U81375 | 602193 | GEN-3VO | Human placental<br>equilibrative nucleoside<br>transporter 1 (hENT1)<br>mRNA, complete cds | 1989 | 1811G>A | 3     |
| U81375 | U81375 | 602193 | GEN-3VO | Human placental<br>equilibrative nucleoside<br>transporter 1 (hENT1)<br>mRNA, complete cds | 1996 | 1818C>T | 3     |
| U81375 | U81375 | 602193 | GEN-3VO | Human placental<br>equilibrative nucleoside<br>transporter 1 (hENT1)<br>mRNA, complete cds | 2045 | 1867T>C | 3     |
| U82812 | U82812 | 602592 | GEN-3X7 | Human scavenger receptor<br>cysteine rich Sp alpha<br>mRNA, complete cds                   | 1280 | 1220T>A | 3     |
| U96781 | U96781 | 108730 | GEN-MQL | ATPase, Ca++<br>transporting, cardiac<br>muscle, fast twitch 1                             | 3007 | 3007G>A | 3     |



|        |        |        |        |                                             |          |       |
|--------|--------|--------|--------|---------------------------------------------|----------|-------|
| HBA1   | V00493 | 141800 | GEN-TK | Human messenger RNA 198<br>for alpha globin | 161C>T   | A54V  |
| HBA1   | V00493 | 141800 | GEN-TK | Human messenger RNA 244<br>for alpha globin | 207C>A   | N69K  |
| HBA1   | V00493 | 141800 | GEN-TK | Human messenger RNA 307<br>for alpha globin | 270C>A   | H90Q  |
| HBA1   | V00493 | 141800 | GEN-TK | Human messenger RNA 314<br>for alpha globin | 277C>T   | R93W  |
| HBA1   | V00493 | 141800 | GEN-TK | Human messenger RNA 326<br>for alpha globin | 289G>T   | V97F  |
| HBA1   | V00493 | 141800 | GEN-TK | Human messenger RNA 393<br>for alpha globin | 356C>A   | T119N |
| HBA1   | V00493 | 141800 | GEN-TK | Human messenger RNA 399<br>for alpha globin | 362C>G   | A121G |
| HBA1   | V00493 | 141800 | GEN-TK | Human messenger RNA 418<br>for alpha globin | 381C>A   | D127E |
| HBA1   | V00493 | 141800 | GEN-TK | Human messenger RNA 481<br>for alpha globin | 444A>G   | 3     |
| V00497 | V00497 | 141900 | GEN-P1 | Human messenger RNA 59<br>for beta-globin   | 9C>T     | S     |
| V00497 | V00497 | 141900 | GEN-P1 | Human messenger RNA 257<br>for beta-globin  | 207C>A   | S     |
| V00497 | V00497 | 141900 | GEN-P1 | Human messenger RNA 284<br>for beta-globin  | 234C>A   | H78Q  |
| V00497 | V00497 | 141900 | GEN-P1 | Human messenger RNA 304<br>for beta-globin  | 254C>A   | T85N  |
| V00497 | V00497 | 141900 | GEN-P1 | Human messenger RNA 370<br>for beta-globin  | 320T>C   | L107P |
| V00497 | V00497 | 141900 | GEN-P1 | Human messenger RNA 385<br>for beta-globin  | 335T>G   | V112G |
| V00497 | V00497 | 141900 | GEN-P1 | Human messenger RNA 529<br>for beta-globin  | 479T>G   | 3     |
| V00497 | V00497 | 141900 | GEN-P1 | Human messenger RNA 537<br>for beta-globin  | 487T>G   | 3     |
| V00519 | V00519 | 139250 | GEN-4U | Growth hormone 1 299                        | 259C>A   | P87T  |
| V00519 | V00519 | 139250 | GEN-4U | Growth hormone 1 524                        | 484G>T   | G162W |
| X00568 | X00568 | 207750 | GEN-6Z | Apolipoprotein C-II 70                      | 70C>A    | Q24K  |
| X01060 | X01060 | 190010 | GEN-6C | Transferrin receptor (p90, 687<br>CD71)     | 424A>G   | S142G |
| X01060 | X01060 | 190010 | GEN-6C | Transferrin receptor (p90, 2823<br>CD71)    | 2560delT | F     |

|        |        |        |         |                                                                                |           |       |
|--------|--------|--------|---------|--------------------------------------------------------------------------------|-----------|-------|
| X01060 | X01060 | 190010 | GEN-6C  | Transferrin receptor (p90, 3766 CD71)                                          | 3503T>G   | 3     |
| X01060 | X01060 | 190010 | GEN-6C  | Transferrin receptor (p90, 4122 CD71)                                          | 3859A>C   | 3     |
| X01060 | X01060 | 190010 | GEN-6C  | Transferrin receptor (p90, 4147 CD71)                                          | 3884G>A   | 3     |
| X01060 | X01060 | 190010 | GEN-6C  | Transferrin receptor (p90, 4247 CD71)                                          | 3984T>C   | 3     |
| X01060 | X01060 | 190010 | GEN-6C  | Transferrin receptor (p90, 4309 CD71)                                          | 4046T>A   | 3     |
| X01060 | X01060 | 190010 | GEN-6C  | Transferrin receptor (p90, 4381 CD71)                                          | 4118A>G   | 3     |
| X01060 | X01060 | 190010 | GEN-6C  | Transferrin receptor (p90, 4547 CD71)                                          | 4284G>A   | 3     |
| X01060 | X01060 | 190010 | GEN-6C  | Transferrin receptor (p90, 4619 CD71)                                          | 4356T>G   | 3     |
| X01060 | X01060 | 190010 | GEN-6C  | Transferrin receptor (p90, 4726 CD71)                                          | 4463A>T   | 3     |
| X01060 | X01060 | 190010 | GEN-6C  | Transferrin receptor (p90, 4766 CD71)                                          | 4503C>T   | 3     |
| X01586 | X01586 | 147680 | GEN-PC  | Interleukin 2 332                                                              | 225T>G    | H75Q  |
| X01586 | X01586 | 147680 | GEN-PC  | Interleukin 2 563                                                              | 456G>A    | S     |
| X02317 | X02317 | 147450 | GEN-KM  | Superoxide dismutase 1 614 (Cu/Zn)                                             | 550A>C    | 3     |
| X02415 | X02415 | 134850 | GEN-MJ0 | Human gene for fibrinogen 1000 gamma chain                                     | 949G>A    | D317N |
| X02469 | X02469 | 191170 | GEN-PF  | Human mRNA for p53 350 cellular tumor antigen                                  | 215C>G    | P72R  |
| X02469 | X02469 | 191170 | GEN-PF  | Human mRNA for p53 953 cellular tumor antigen                                  | 818G>A    | R273H |
| X02750 | X02750 | 176860 | GEN-4Z  | Anticoagulant Protein C 1600 (inactivator of coagulation factors Va and VIIIa) | 1503G>C   | 3     |
| NRAS   | X02751 | 164790 | GEN-XG  | Human N-ras mRNA and flanking regions 221                                      | (-506)A>G | 5     |
| NRAS   | X02751 | 164790 | GEN-XG  | Human N-ras mRNA and flanking regions 390                                      | (-337)C>A | 5     |
| X02812 | X02812 | 190180 | GEN-XR  | Human mRNA for 870 transforming growth factor-beta (TGF-beta)                  | 29C>T     | P10L  |
| X02812 | X02812 | 190180 | GEN-XR  | Human mRNA for 979                                                             | 138C>G    | I46M  |

|        |        |        |        |                                                                     |      |         |       |
|--------|--------|--------|--------|---------------------------------------------------------------------|------|---------|-------|
| X02812 | X02812 | 190180 | GEN-XR | transforming growth factor-beta (TGF-beta)<br>Human mRNA for        | 1632 | 791C>T  | T264I |
| X02812 | X02812 | 190180 | GEN-XR | transforming growth factor-beta (TGF-beta)<br>Human mRNA for        | 1807 | 966C>T  | S     |
| X02812 | X02812 | 190180 | GEN-XR | transforming growth factor-beta (TGF-beta)<br>Human mRNA for        | 1930 | 1089G>A | S     |
| X02812 | X02812 | 190180 | GEN-XR | transforming growth factor-beta (TGF-beta)<br>Human mRNA for        | 1942 | 1101C>T | S     |
| X02812 | X02812 | 190180 | GEN-XR | transforming growth factor-beta (TGF-beta)<br>Human mRNA for        | 2013 | 1172G>A | S391N |
| X03172 | X03172 | 192340 | GEN-ZM | transforming growth factor-beta (TGF-beta)<br>Human mRNA for        | 379  | 356T>G  | V119G |
| X03438 | X03438 | 138970 | GEN-PM | vasopressin precursor<br>Human mRNA for                             | 586  | 555G>A  | S     |
| X03438 | X03438 | 138970 | GEN-PM | granulocyte colony-stimulating factor (G-CSF)<br>Human mRNA for     | 1235 | 1204C>T | 3     |
| X03635 | X03635 | 133430 | GEN-50 | granulocyte colony-stimulating factor (G-CSF)<br>estrogen receptors | 390  | 30T>C   | S     |
| X03635 | X03635 | 133430 | GEN-50 | estrogen receptors                                                  | 390  | 30T>C   | S     |
| X03635 | X03635 | 133430 | GEN-50 | estrogen receptors                                                  | 424  | 64G>C   | E22Q  |
| X03635 | X03635 | 133430 | GEN-50 | estrogen receptors                                                  | 617  | 257C>T  | A86V  |
| X03635 | X03635 | 133430 | GEN-50 | estrogen receptors                                                  | 621  | 261G>C  | S     |
| X03635 | X03635 | 133430 | GEN-50 | estrogen receptors                                                  | 829  | 469C>T  | F     |
| X03635 | X03635 | 133430 | GEN-50 | estrogen receptors                                                  | 1335 | 975C>G  | S     |
| X03635 | X03635 | 133430 | GEN-50 | estrogen receptors                                                  | 1335 | 975C>G  | S     |
| X03635 | X03635 | 133430 | GEN-50 | estrogen receptors                                                  | 1451 | 1091T>A | V364E |
| X03635 | X03635 | 133430 | GEN-50 | estrogen receptors                                                  | 1674 | 1314G>A | M438I |
| X03635 | X03635 | 133430 | GEN-50 | estrogen receptors                                                  | 2142 | 1782A>G | S     |
| X03635 | X03635 | 133430 | GEN-50 | estrogen receptors                                                  | 2354 | 1994A>G | 3     |
| X03635 | X03635 | 133430 | GEN-50 | estrogen receptors                                                  | 2550 | 2190A>C | 3     |
| X03635 | X03635 | 133430 | GEN-50 | estrogen receptors                                                  | 2733 | 2373C>G | 3     |

|        |        |        |         |                                                                                            |      |                 |      |
|--------|--------|--------|---------|--------------------------------------------------------------------------------------------|------|-----------------|------|
| X03635 | X03635 | 133430 | GEN-50  | estrogen receptors                                                                         | 3181 | 2821T>C         | 3    |
| X03635 | X03635 | 133430 | GEN-50  | estrogen receptors                                                                         | 3338 | 2978C>T         | 3    |
| X03635 | X03635 | 133430 | GEN-50  | estrogen receptors                                                                         | 3652 | 3292-3294CCT>CC | 3    |
| X03635 | X03635 | 133430 | GEN-50  | estrogen receptors                                                                         | 3652 | T               | 3    |
| X03635 | X03635 | 133430 | GEN-50  | estrogen receptors                                                                         | 3896 | 3292-3294delCCT | 3    |
| X03635 | X03635 | 133430 | GEN-50  | estrogen receptors                                                                         | 4378 | 3536C>A         | 3    |
| X03635 | X03635 | 133430 | GEN-50  | estrogen receptors                                                                         | 6287 | 4018T>C         | 3    |
| X03663 | X03663 | 164770 | GEN-51  | Colony stimulating factor 1 receptor                                                       | 3732 | 5927T>C         | 3    |
| X03663 | X03663 | 164770 | GEN-51  | Colony stimulating factor 1 receptor                                                       | 3951 | 3432T>C         | 3    |
| X03747 | X03747 | 182330 | GEN-KR  | ATPase, Na+/K+ transporting, beta 1 polypeptide                                            | 447  | 3651C>A         | 3    |
| X03747 | X03747 | 182330 | GEN-KR  | ATPase, Na+/K+ transporting, beta 1 polypeptide                                            | 1516 | 321G>A          | S    |
| X03747 | X03747 | 182330 | GEN-KR  | ATPase, Na+/K+ transporting, beta 1 polypeptide                                            | 2182 | 1390G>T         | 3    |
| CYBB   | X04011 | 306400 | GEN-13S | Human mRNA of X-CGD gene involved in chronic granulomatous disease located on chromosome X | 2517 | 2056C>T         | 3    |
| CYBB   | X04011 | 306400 | GEN-13S | Human mRNA of X-CGD gene involved in chronic granulomatous disease located on chromosome X | 2544 | 2310A>G         | 3    |
| CYBB   | X04011 | 306400 | GEN-13S | Human mRNA of X-CGD gene involved in chronic granulomatous disease located on chromosome X | 2831 | 2337A>T         | 3    |
| CAT    | X04076 | 115500 | GEN-13P | Human kidney mRNA for catalase                                                             | 51   | 2624T>C         | 3    |
| CAT    | X04076 | 115500 | GEN-13P | Human kidney mRNA for catalase                                                             | 218  | (-20)T>C        | 5    |
| CAT    | X04076 | 115500 | GEN-13P | Human kidney mRNA for catalase                                                             | 1237 | 148C>T          | L50F |
|        |        |        |         |                                                                                            |      | 1167T>C         | S    |

|        |        |        |                |                                                          |      |         |       |
|--------|--------|--------|----------------|----------------------------------------------------------|------|---------|-------|
| CAT    | X04076 | 115500 | 13P<br>GEN-13P | catalase<br>Human kidney mRNA for                        | 1325 | 1255C>T | S     |
| CAT    | X04076 | 115500 | GEN-13P        | catalase<br>Human kidney mRNA for                        | 2131 | 2061A>C | 3     |
| HMBS   | X04217 | 176000 | GEN-145        | catalase<br>Human mRNA for                               | 121  | 40G>T   | A14S  |
|        |        |        |                | porphobilinogen<br>deaminase (PBG-D, EC                  |      |         |       |
|        |        |        |                | 4.3.1.8)                                                 |      |         |       |
| X04409 | X04409 | 139320 | GEN-7Q         | Guanine nucleotide binding<br>protein (G protein), alpha | 363  | 351C>T  | S     |
|        |        |        |                | stimulating activity                                     |      |         |       |
| X04409 | X04409 | 139320 | GEN-7Q         | polypeptide 1<br>Guanine nucleotide binding              | 525  | 513C>T  | S     |
|        |        |        |                | protein (G protein), alpha                               |      |         |       |
|        |        |        |                | stimulating activity                                     |      |         |       |
| X04409 | X04409 | 139320 | GEN-7Q         | polypeptide 1<br>Guanine nucleotide binding              | 967  | 955C>A  | R319S |
|        |        |        |                | protein (G protein), alpha                               |      |         |       |
|        |        |        |                | stimulating activity                                     |      |         |       |
| X04409 | X04409 | 139320 | GEN-7Q         | polypeptide 1<br>Guanine nucleotide binding              | 1023 | 1011C>A | S     |
|        |        |        |                | protein (G protein), alpha                               |      |         |       |
|        |        |        |                | stimulating activity                                     |      |         |       |
| X04409 | X04409 | 139320 | GEN-7Q         | polypeptide 1<br>Guanine nucleotide binding              | 1083 | 1071C>T | S     |
|        |        |        |                | protein (G protein), alpha                               |      |         |       |
|        |        |        |                | stimulating activity                                     |      |         |       |
| X04409 | X04409 | 139320 | GEN-7Q         | polypeptide 1<br>Guanine nucleotide binding              | 1213 | 1201T>G | 3     |
|        |        |        |                | protein (G protein), alpha                               |      |         |       |
|        |        |        |                | stimulating activity                                     |      |         |       |
| X04409 | X04409 | 139320 | GEN-7Q         | polypeptide 1<br>Guanine nucleotide binding              | 1450 | 1438A>C | 3     |
|        |        |        |                | protein (G protein), alpha                               |      |         |       |
|        |        |        |                | stimulating activity                                     |      |         |       |
| X04526 | X04526 | 139380 | GEN-7R         | polypeptide 1<br>Guanine nucleotide binding              | 426  | 146G>C  | R49T  |
|        |        |        |                | protein (G protein), beta                                |      |         |       |
| THBS1  | X04665 | 188060 | GEN-151        | polypeptide 1<br>Human mRNA for                          | 145  | 70T>G   | S24A  |

|        |        |        |         |                                                        |          |   |
|--------|--------|--------|---------|--------------------------------------------------------|----------|---|
| THBS1  | X04665 | 188060 | GEN-151 | thrombospondin<br>Human mRNA for 903                   | 828G>A   | S |
| THBS1  | X04665 | 188060 | GEN-151 | thrombospondin<br>Human mRNA for 1485                  | 1410C>T  | S |
| THBS1  | X04665 | 188060 | GEN-151 | thrombospondin<br>Human mRNA for 3667                  | 3592C>T  | 3 |
| THBS1  | X04665 | 188060 | GEN-151 | thrombospondin<br>Human mRNA for 3866                  | 3791G>A  | 3 |
| X05199 | X05199 | 173350 | GEN-PU  | thrombospondin<br>Human mRNA for 384                   | 330C>T   | S |
| X05199 | X05199 | 173350 | GEN-PU  | plasminogen<br>Human mRNA for 825                      | 771C>T   | S |
| X05199 | X05199 | 173350 | GEN-PU  | plasminogen<br>Human mRNA for 996                      | 942C>T   | S |
| X05199 | X05199 | 173350 | GEN-PU  | plasminogen<br>Human mRNA for 1137                     | 1083A>G  | S |
| X05199 | X05199 | 173350 | GEN-PU  | plasminogen<br>Human mRNA for 1485                     | 1431C>T  | S |
| X05199 | X05199 | 173350 | GEN-PU  | plasminogen<br>Human mRNA for 2340                     | 2286T>G  | S |
| X05199 | X05199 | 173350 | GEN-PU  | plasminogen<br>Human mRNA for 2532                     | 2478G>A  | 3 |
| X05199 | X05199 | 173350 | GEN-PU  | plasminogen<br>Human mRNA for 2606                     | 2552T>G  | 3 |
| X06318 | X06318 | 176970 | GEN-KY  | plasminogen<br>Protein kinase C, beta 1 83             | (-54)G>C | 5 |
| X06318 | X06318 | 176970 | GEN-KY  | Protein kinase C, beta 1 940                           | 804G>A   | S |
| X06318 | X06318 | 176970 | GEN-KY  | Protein kinase C, beta 1 1327                          | 1191T>C  | S |
| X06318 | X06318 | 176970 | GEN-KY  | Protein kinase C, beta 1 1906                          | 1770C>T  | S |
| PDGFA  | X06374 | 173430 | GEN-19E | Human mRNA for platelet-derived growth factor PDGF-A   | 1820C>T  | 3 |
| PDGFA  | X06374 | 173430 | GEN-19E | Human mRNA for platelet-derived growth factor PDGF-A   | 1864C>T  | 3 |
| RAF1   | X06409 | 164760 | GEN-19K | Human mRNA fragment for activated c-raf-1 (exons 8-17) | 487T>C   | 3 |
| RAF1   | X06409 | 164760 | GEN-19K | Human mRNA fragment for activated c-raf-1 (exons 8-17) | 1948C>T  | 3 |

|        |        |        |         |                                                             |         |       |
|--------|--------|--------|---------|-------------------------------------------------------------|---------|-------|
| RAF1   | X06409 | 164760 | GEN-19K | Human mRNA fragment for activated c-raf-1 (exons 8-17)      | 1993C>A | 3     |
| X06562 | X06562 | 600946 | GEN-6D  | Growth hormone receptor                                     | 3349A>T | 3     |
| X06562 | X06562 | 600946 | GEN-6D  | Growth hormone receptor                                     | 4102G>A | 3     |
| X07523 | X07523 | 134371 | GEN-1E5 | Human mRNA for truncated form of complement factor H        | 1097G>A | G366E |
| X07523 | X07523 | 134371 | GEN-1E5 | Human mRNA for truncated form of complement factor H        | 1204T>C | Y402H |
| SOD2   | X07834 | 147460 | GEN-1ES | Human mRNA for manganese superoxide dismutase (EC 1.15.1.1) | 40C>G   | P14A  |
| SOD2   | X07834 | 147460 | GEN-1ES | Human mRNA for manganese superoxide dismutase (EC 1.15.1.1) | 47T>C   | V16A  |
| SOD2   | X07834 | 147460 | GEN-1ES | Human mRNA for manganese superoxide dismutase (EC 1.15.1.1) | 194C>A  | T65N  |
| SOD2   | X07834 | 147460 | GEN-1ES | Human mRNA for manganese superoxide dismutase (EC 1.15.1.1) | 245T>C  | I82T  |
| TNNC1  | X07897 | 191040 | GEN-1EW | Human mRNA for slow skeletal troponin C (TnC)               | 208G>C  | G70R  |
| TNNC1  | X07897 | 191040 | GEN-1EW | Human mRNA for slow skeletal troponin C (TnC)               | 223G>T  | D75Y  |
| ITGB1  | X07979 | 135630 | GEN-4E5 | Human mRNA for fibronectin receptor beta subunit            | 1086A>C | S     |
| ITGB1  | X07979 | 135630 | GEN-4E5 | Human mRNA for fibronectin receptor beta subunit            | 1176A>C | S     |
| ITGB1  | X07979 | 135630 | GEN-4E5 | Human mRNA for fibronectin receptor beta subunit            | 2610T>C | 3     |
| ITGB1  | X07979 | 135630 | GEN-4E5 | Human mRNA for fibronectin receptor beta subunit            | 2775T>A | 3     |
| ITGB1  | X07979 | 135630 | GEN-4E5 | Human mRNA for fibronectin receptor beta subunit            | 3236A>G | 3     |

|        |        |        |         |                                                             |         |       |
|--------|--------|--------|---------|-------------------------------------------------------------|---------|-------|
| ITGB1  | X07979 | 135630 | 4E5     | fibronectin receptor beta subunit                           | 3428G>A | 3     |
| ANX5   | X12454 | 131230 | GEN-4E5 | Human mRNA for fibronectin receptor beta subunit            | (-1)C>T | 5     |
| ANX5   | X12454 | 131230 | GEN-1M2 | Human mRNA for vascular anticoagulant                       | 1285T>G | 3     |
| ANX5   | X12454 | 131230 | GEN-1M2 | Human mRNA for vascular anticoagulant                       | 1303C>T | 3     |
| ANX5   | X12454 | 131230 | GEN-1M2 | Human mRNA for vascular anticoagulant                       | 1390G>A | 3     |
| X13561 | X13561 | 147910 | GEN-1OH | Human mRNA for 54 preprokallikrein (EC 3.4.21)              | 18G>T   | S     |
| X13561 | X13561 | 147910 | GEN-1OH | Human mRNA for 441 preprokallikrein (EC 3.4.21)             | 405T>C  | S     |
| X13561 | X13561 | 147910 | GEN-1OH | Human mRNA for 469 preprokallikrein (EC 3.4.21)             | 433G>C  | E145Q |
| X13561 | X13561 | 147910 | GEN-1OH | Human mRNA for 592 preprokallikrein (EC 3.4.21)             | 556A>G  | K186E |
| X13589 | X13589 | 107910 | GEN-56  | Cytochrome P450, subfamily XIX (aromatization of androgens) | 240A>G  | S     |
| X13589 | X13589 | 107910 | GEN-56  | Cytochrome P450, subfamily XIX (aromatization of androgens) | 790C>T  | R264C |
| X13589 | X13589 | 107910 | GEN-56  | Cytochrome P450, subfamily XIX (aromatization of androgens) | 790C>T  | R264C |
| X13589 | X13589 | 107910 | GEN-56  | Cytochrome P450, subfamily XIX (aromatization of androgens) | 1531C>T | 3     |
| X13589 | X13589 | 107910 | GEN-56  | Cytochrome P450, subfamily XIX (aromatization of androgens) | 1672G>T | 3     |



|        |        |        |             |                                                                                                  |      |                      |        |
|--------|--------|--------|-------------|--------------------------------------------------------------------------------------------------|------|----------------------|--------|
| X13629 | X13629 | 107690 | GEN-<br>100 | Human intestinal mRNA for<br>apolipoprotein A-IV                                                 | 881  | 836G>A               | R279K  |
| X13629 | X13629 | 107690 | GEN-<br>100 | Human intestinal mRNA for<br>apolipoprotein A-IV                                                 | 1185 | 1140G>T              | Q380H  |
| X13629 | X13629 | 107690 | GEN-<br>100 | Human intestinal mRNA for<br>apolipoprotein A-IV                                                 | 1302 | 1257*1258ins<br>CTGT | F      |
| X13916 | X13916 | 107770 | GEN-<br>1Q1 | Human mRNA for LDL-<br>receptor related protein                                                  | 1636 | 1170T>C              | S      |
| X13916 | X13916 | 107770 | GEN-<br>1Q1 | Human mRNA for LDL-<br>receptor related protein                                                  | 1675 | 1209C>T              | S      |
| X13916 | X13916 | 107770 | GEN-<br>1Q1 | Human mRNA for LDL-<br>receptor related protein                                                  | 2805 | 2339C>T              | T780I  |
| X13916 | X13916 | 107770 | GEN-<br>1Q1 | Human mRNA for LDL-<br>receptor related protein                                                  | 3853 | 3387T>C              | S      |
| X13916 | X13916 | 107770 | GEN-<br>1Q1 | Human mRNA for LDL-<br>receptor related protein                                                  | 6443 | 5977C>T              | R1993W |
| X13916 | X13916 | 107770 | GEN-<br>1Q1 | Human mRNA for LDL-<br>receptor related protein                                                  | 7036 | 6570C>T              | S      |
| X13916 | X13916 | 107770 | GEN-<br>1Q1 | Human mRNA for LDL-<br>receptor related protein                                                  | 8608 | 8142G>A              | S      |
| X13916 | X13916 | 107770 | GEN-<br>1Q1 | Human mRNA for LDL-<br>receptor related protein                                                  | 8923 | 8457C>T              | S      |
| X13916 | X13916 | 107770 | GEN-<br>1Q1 | Human mRNA for LDL-<br>receptor related protein                                                  | 9034 | 8568G>T              | S      |
| X13916 | X13916 | 107770 | GEN-<br>1Q1 | Human mRNA for LDL-<br>receptor related protein                                                  | 9040 | 8574C>T              | S      |
| X13916 | X13916 | 107770 | GEN-<br>1Q1 | Human mRNA for LDL-<br>receptor related protein                                                  | 9391 | 8925T>C              | S      |
| CLU    | X14723 | 185430 | GEN-<br>1SB | Human SP-40,40 mRNA<br>for complement-associated<br>protein SP-40,40 alpha-1<br>and beta-1 chain | 131  | 84C>T                | S      |
| CLU    | X14723 | 185430 | GEN-<br>1SB | Human SP-40,40 mRNA<br>for complement-associated<br>protein SP-40,40 alpha-1<br>and beta-1 chain | 429  | 382G>T               | V128F  |
| CLU    | X14723 | 185430 | GEN-<br>1SB | Human SP-40,40 mRNA<br>for complement-associated<br>protein SP-40,40 alpha-1<br>and beta-1 chain | 836  | 789C>T               | S      |
| CLU    | X14723 | 185430 | GEN-<br>1SB | Human SP-40,40 mRNA<br>for complement-associated<br>protein SP-40,40 alpha-1<br>and beta-1 chain | 1234 | 1187C>T              | S396L  |

|                                                                         |        |        |         |                                                                                         |                |
|-------------------------------------------------------------------------|--------|--------|---------|-----------------------------------------------------------------------------------------|----------------|
| 1SB for complement-associated protein SP-40,40 alpha-1 and beta-1 chain |        |        |         |                                                                                         |                |
| CLU                                                                     | X14723 | 185430 | GEN-1SB | Human SP-40,40 mRNA for complement-associated protein SP-40,40 alpha-1 and beta-1 chain | 1372           |
|                                                                         |        |        |         |                                                                                         | 1325A>T Y442F  |
| CLU                                                                     | X14723 | 185430 | GEN-1SB | Human SP-40,40 mRNA for complement-associated protein SP-40,40 alpha-1 and beta-1 chain | 1482           |
|                                                                         |        |        |         |                                                                                         | 1435C>T 3      |
| CLU                                                                     | X14723 | 185430 | GEN-1SB | Human SP-40,40 mRNA for complement-associated protein SP-40,40 alpha-1 and beta-1 chain | 1548           |
|                                                                         |        |        |         |                                                                                         | 1501C>T 3      |
| CLU                                                                     | X14723 | 185430 | GEN-1SB | Human SP-40,40 mRNA for complement-associated protein SP-40,40 alpha-1 and beta-1 chain | 1645           |
|                                                                         |        |        |         |                                                                                         | 1598A>T 3      |
| CHRNA1                                                                  | X14830 | 100710 | GEN-4EK | Nicotinic, Cholinergic receptor beta 1                                                  | 1375           |
|                                                                         |        |        |         |                                                                                         | 1359C>T S      |
| CHRNA1                                                                  | X14830 | 100710 | GEN-4EK | Nicotinic, Cholinergic receptor beta 1                                                  | 1591           |
|                                                                         |        |        |         |                                                                                         | 1575T>C 3      |
| X15263                                                                  | X15263 | None   | GEN-4EQ | Muscarinic receptor, CHRM1                                                              | 1144           |
|                                                                         |        |        |         |                                                                                         | 1044G>A S      |
| X15357                                                                  | X15357 | 108960 | GEN-KUV | Human mRNA for natriuretic peptide receptor (ANP-A receptor)                            | 1066           |
|                                                                         |        |        |         |                                                                                         | 1023G>C M341I  |
| X15357                                                                  | X15357 | 108960 | GEN-KUV | Human mRNA for natriuretic peptide receptor (ANP-A receptor)                            | 1657           |
|                                                                         |        |        |         |                                                                                         | 1614C>T S      |
| X15357                                                                  | X15357 | 108960 | GEN-KUV | Human mRNA for natriuretic peptide receptor (ANP-A receptor)                            | 2859           |
|                                                                         |        |        |         |                                                                                         | 2816G>A R939Q  |
| X15357                                                                  | X15357 | 108960 | GEN-KUV | Human mRNA for natriuretic peptide receptor (ANP-A receptor)                            | 2983           |
|                                                                         |        |        |         |                                                                                         | 2940G>A S      |
| X15357                                                                  | X15357 | 108960 | GEN-KUV | Human mRNA for natriuretic peptide receptor (ANP-A receptor)                            | 3259           |
|                                                                         |        |        |         |                                                                                         | 3216delC F     |
| X15357                                                                  | X15357 | 108960 | GEN-KUV | Human mRNA for natriuretic peptide receptor (ANP-A receptor)                            | 3589           |
|                                                                         |        |        |         |                                                                                         | 3546^3547ins F |

|        |        | KUV     | natriuretic peptide receptor<br>(ANP-A receptor)    |          | GAAA |  |
|--------|--------|---------|-----------------------------------------------------|----------|------|--|
| PACE   | X17094 | GEN-12V | Human fur mRNA for furin 399                        | 183C>T   | S    |  |
| PACE   | X17094 | GEN-12V | Human fur mRNA for furin 1692                       | 1476C>T  | S    |  |
| PACE   | X17094 | GEN-12V | Human fur mRNA for furin 2067                       | 1851C>G  | S    |  |
| PACE   | X17094 | GEN-12V | Human fur mRNA for furin 2725                       | 2509T>C  | 3    |  |
| PACE   | X17094 | GEN-12V | Human fur mRNA for furin 2855                       | 2639C>A  | 3    |  |
| PACE   | X17094 | GEN-12V | Human fur mRNA for furin 2988                       | 2772G>A  | 3    |  |
| PACE   | X17094 | GEN-12V | Human fur mRNA for furin 3234                       | 3018C>T  | 3    |  |
| PACE   | X17094 | GEN-12V | Human fur mRNA for furin 3625                       | 3409A>G  | 3    |  |
| PACE   | X17094 | GEN-12V | Human fur mRNA for furin 3883                       | 3667C>T  | 3    |  |
| PACE   | X17094 | GEN-12V | Human fur mRNA for furin 4053                       | 3837A>G  | 3    |  |
| X51362 | X51362 | GEN-31W | Dopamine Receptor D2 588                            | 423G>A   | S    |  |
| X51362 | X51362 | GEN-31W | Dopamine Receptor D2 1104                           | 939C>T   | S    |  |
| X51362 | X51362 | GEN-31W | Dopamine Receptor D2 1122                           | 957T>C   | S    |  |
| X51362 | X51362 | GEN-31W | Dopamine Receptor D2 1248                           | 1083A>G  | S    |  |
| X51362 | X51362 | GEN-31W | Dopamine Receptor D2 1488                           | 1323T>C  | S    |  |
| X51362 | X51362 | GEN-31W | Dopamine Receptor D2 1548                           | 1383A>G  | 3    |  |
| X51362 | X51362 | GEN-31W | Dopamine Receptor D2 2361                           | 2196C>T  | 3    |  |
| X51416 | X51416 | GEN-57  | STEROID HORMONE RECEPTOR ERR1                       | 2222G>A  | 3    |  |
| FLT1   | X51602 | GEN-329 | Human flt mRNA for receptor-related tyrosine kinase | (-58)C>T | 5    |  |

|       |        |        |         |                                                              |      |                     |       |
|-------|--------|--------|---------|--------------------------------------------------------------|------|---------------------|-------|
| FLT1  | X51602 | 165070 | GEN-329 | Human flt mRNA for<br>receptor-related tyrosine<br>kinase    | 1723 | 1474C>T             | S     |
| FLT1  | X51602 | 165070 | GEN-329 | Human flt mRNA for<br>receptor-related tyrosine<br>kinase    | 1953 | 1704G>A             | S     |
| FLT1  | X51602 | 165070 | GEN-329 | Human flt mRNA for<br>receptor-related tyrosine<br>kinase    | 3061 | 2812A>G             | M938V |
| FLT1  | X51602 | 165070 | GEN-329 | Human flt mRNA for<br>receptor-related tyrosine<br>kinase    | 3150 | 2901G>A             | S     |
| FLT1  | X51602 | 165070 | GEN-329 | Human flt mRNA for<br>receptor-related tyrosine<br>kinase    | 4497 | 4248T>G             | 3     |
| FLT1  | X51602 | 165070 | GEN-329 | Human flt mRNA for<br>receptor-related tyrosine<br>kinase    | 5295 | 5046*5047ins<br>GAG | 3     |
| FLT1  | X51602 | 165070 | GEN-329 | Human flt mRNA for<br>receptor-related tyrosine<br>kinase    | 6976 | 6727G>A             | 3     |
| FLT1  | X51602 | 165070 | GEN-329 | Human flt mRNA for<br>receptor-related tyrosine<br>kinase    | 7013 | 6764T>G             | 3     |
| FGFR1 | X51803 | 136350 | GEN-32G | Human mRNA for<br>fibroblast growth factor<br>(FGF) receptor | 276  | 159T>G              | S     |
| EDN3  | X52001 | 131242 | GEN-33E | Endothelin 3                                                 | 1262 | 1152G>A             | 3     |
| EDN3  | X52001 | 131242 | GEN-33E | Endothelin 3                                                 | 1649 | 1539C>G             | 3     |
| EDN3  | X52001 | 131242 | GEN-33E | Endothelin 3                                                 | 1700 | 1590C>T             | 3     |
| EDN3  | X52001 | 131242 | GEN-33E | Endothelin 3                                                 | 1742 | 1632C>T             | 3     |
| EDN3  | X52001 | 131242 | GEN-33E | Endothelin 3                                                 | 1797 | 1687C>T             | 3     |
| EDN3  | X52001 | 131242 | GEN-33E | Endothelin 3                                                 | 1914 | 1804G>C             | 3     |
| EDN3  | X52001 | 131242 | GEN-33E | Endothelin 3                                                 | 2040 | 1930C>T             | 3     |

|        |        |        |         |                                                                  |      |         |       |
|--------|--------|--------|---------|------------------------------------------------------------------|------|---------|-------|
| X52425 | X52425 | 147781 | GEN-59  | Interleukin 4 receptor                                           | 3044 | 2869G>A | 3     |
| X52425 | X52425 | 147781 | GEN-59  | Interleukin 4 receptor                                           | 3289 | 3114A>G | 3     |
| X52425 | X52425 | 147781 | GEN-59  | Interleukin 4 receptor                                           | 3391 | 3216C>T | 3     |
| X52479 | X52479 | 176960 | GEN-LM  | Protein kinase C, alpha                                          | 908  | 881A>C  | D294A |
| FGFR2  | X52832 | 176943 | GEN-341 | Human bek mRNA for fibroblast growth factor receptor-BEK         | 338  | 159A>G  | S     |
| FGFR2  | X52832 | 176943 | GEN-341 | Human bek mRNA for fibroblast growth factor receptor-BEK         | 2903 | 2724A>T | 3     |
| CHRNA3 | X53559 | 118503 | GEN-341 | Nicotinic, Cholinergic receptor alpha 3                          | 212  | 212A>G  | D71G  |
| CHRNA3 | X53559 | 118503 | GEN-341 | Nicotinic, Cholinergic receptor alpha 3                          | 552  | 552C>T  | S     |
| TNNI3  | X54163 | 191044 | GEN-34U | Human mRNA for cardiac troponin I                                | 626  | 537G>A  | S     |
| FGFR4  | X57205 | 134935 | GEN-37M | Human FGFR-4 mRNA for fibroblast growth factor receptor (FGFR-4) | 83   | 28G>A   | V10I  |
| FGFR4  | X57205 | 134935 | GEN-37M | Human FGFR-4 mRNA for fibroblast growth factor receptor (FGFR-4) | 217  | 162T>G  | S     |
| YWHAB  | X57346 | 601289 | GEN-37R | H.sapiens mRNA for HS1 protein                                   | 432  | 60C>A   | S     |
| YWHAB  | X57346 | 601289 | GEN-37R | H.sapiens mRNA for HS1 protein                                   | 1135 | 763T>C  | 3     |
| X57830 | X57830 | 182135 | GEN-7V  | Serotonin 5-HT2 receptor                                         | 247  | 102T>C  | S     |
| GPX3   | X58295 | 138321 | GEN-38S | Human GPx-3 mRNA for plasma glutathione peroxidase               | 821  | 773C>T  | 3     |
| GPX3   | X58295 | 138321 | GEN-38S | Human GPx-3 mRNA for plasma glutathione peroxidase               | 979  | 931G>A  | 3     |
| GPX3   | X58295 | 138321 | GEN-38S | Human GPx-3 mRNA for plasma glutathione peroxidase               | 1187 | 1139T>G | 3     |
| GPX3   | X58295 | 138321 | GEN-38S | Human GPx-3 mRNA for plasma glutathione peroxidase               | 1354 | 1306C>T | 3     |
| GPX3   | X58295 | 138321 | GEN-38S | Human GPx-3 mRNA for plasma glutathione peroxidase               | 1443 | 1395C>T | 3     |

|         |                                                     |                                                     |      |           |       |
|---------|-----------------------------------------------------|-----------------------------------------------------|------|-----------|-------|
| 38S     | plasma glutathione peroxidase                       | Human GPx-3 mRNA for plasma glutathione peroxidase  | 1516 | 1468C>A   | 3     |
| GEN-38S |                                                     |                                                     |      |           |       |
| 38S     | plasma glutathione peroxidase                       | Human GPx-3 mRNA for plasma glutathione peroxidase  | 1581 | 1533C>T   | 3     |
| GEN-38S |                                                     |                                                     |      |           |       |
| 38S     | plasma glutathione peroxidase                       | Interleukin 11                                      | 807  | 744A>G    | 3     |
| GEN-38V |                                                     |                                                     |      |           |       |
| 38V     | Interleukin 11                                      | Interleukin 11                                      | 927  | 864T>G    | 3     |
| GEN-38V |                                                     |                                                     |      |           |       |
| 38V     | Interleukin 11                                      | Interleukin 11                                      | 1964 | 1901T>C   | 3     |
| GEN-38V |                                                     |                                                     |      |           |       |
| 38V     | D1 dopaminergic receptor                            | D1 dopaminergic receptor                            | 229  | (-48)A>G  | 5     |
| GEN-4EH |                                                     |                                                     |      |           |       |
| 4EH     | D1 dopaminergic receptor                            | D1 dopaminergic receptor                            | 366  | 90G>A     | S     |
| GEN-4EH |                                                     |                                                     |      |           |       |
| 4EH     | D1 dopaminergic receptor                            | D1 dopaminergic receptor                            | 474  | 198G>A    | S     |
| GEN-4EH |                                                     |                                                     |      |           |       |
| 4EH     | D1 dopaminergic receptor                            | D1 dopaminergic receptor                            | 1539 | 1263G>A   | S     |
| GEN-4EH |                                                     |                                                     |      |           |       |
| 4EH     | D1 dopaminergic receptor                            | D1 dopaminergic receptor                            | 2040 | 1764A>C   | 3     |
| GEN-4EH |                                                     |                                                     |      |           |       |
| 4EH     | D1 dopaminergic receptor                            | D1 dopaminergic receptor                            | 2045 | 1769C>A   | 3     |
| GEN-4EH |                                                     |                                                     |      |           |       |
| 4EH     | Human PBX2 mRNA                                     | Human PBX2 mRNA                                     | 2339 | 2043T>G   | 3     |
| GEN-3A3 |                                                     |                                                     |      |           |       |
| 3A3     | Human mRNA for pancreatic gamma-glutamyltransferase | Human mRNA for pancreatic gamma-glutamyltransferase | 102  | (-257)G>A | 5     |
| GEN-3AJ |                                                     |                                                     |      |           |       |
| 3AJ     | Human mRNA for pancreatic gamma-glutamyltransferase | Human mRNA for pancreatic gamma-glutamyltransferase | 336  | (-23)C>T  | 5     |
| GEN-3AJ |                                                     |                                                     |      |           |       |
| 3AJ     | Human mRNA for pancreatic gamma-glutamyltransferase | Human mRNA for pancreatic gamma-glutamyltransferase | 1173 | 815C>T    | A272V |
| GEN-3AJ |                                                     |                                                     |      |           |       |
| 3AJ     | Human mRNA for pancreatic gamma-glutamyltransferase | Human mRNA for pancreatic gamma-glutamyltransferase | 1173 | 815C>T    | A272V |
| GEN-3AJ |                                                     |                                                     |      |           |       |
| 3AJ     | Human mRNA for pancreatic gamma-glutamyltransferase | Human mRNA for pancreatic gamma-glutamyltransferase | 1399 | 1041C>T   | S     |
| GEN-3AJ |                                                     |                                                     |      |           |       |
| 3AJ     |                                                     |                                                     |      |           |       |

|        |        |        |         |                                                          |         |       |
|--------|--------|--------|---------|----------------------------------------------------------|---------|-------|
| X60069 | X60069 | 231950 | GEN-3AJ | pancreatic gamma-glutamyltransferase Human mRNA for 1409 | 1051G>T | A351S |
| X60069 | X60069 | 231950 | GEN-3AJ | pancreatic gamma-glutamyltransferase Human mRNA for 1482 | 1124C>T | T375M |
| X60069 | X60069 | 231950 | GEN-3AJ | pancreatic gamma-glutamyltransferase Human mRNA for 1591 | 1233G>A | S     |
| X60069 | X60069 | 231950 | GEN-3AJ | pancreatic gamma-glutamyltransferase Human mRNA for 1624 | 1266C>T | S     |
| X60069 | X60069 | 231950 | GEN-3AJ | pancreatic gamma-glutamyltransferase Human mRNA for 1637 | 1279C>A | P427T |
| X60069 | X60069 | 231950 | GEN-3AJ | pancreatic gamma-glutamyltransferase Human mRNA for 1651 | 1293C>T | S     |
| X60069 | X60069 | 231950 | GEN-3AJ | pancreatic gamma-glutamyltransferase Human mRNA for 1662 | 1304T>C | V435A |
| X60069 | X60069 | 231950 | GEN-3AJ | pancreatic gamma-glutamyltransferase Human mRNA for 1783 | 1425A>G | S     |
| X60069 | X60069 | 231950 | GEN-3AJ | pancreatic gamma-glutamyltransferase Human mRNA for 1794 | 1436C>T | T479M |
| X60069 | X60069 | 231950 | GEN-3AJ | pancreatic gamma-glutamyltransferase Human mRNA for 1795 | 1437G>A | S     |
| X60069 | X60069 | 231950 | GEN-3AJ | pancreatic gamma-glutamyltransferase Human mRNA for 1981 | 1623C>T | S     |
| X60069 | X60069 | 231950 | GEN-3AJ | pancreatic gamma-glutamyltransferase Human mRNA for 2007 | 1649C>T | T550M |
| X60069 | X60069 | 231950 | GEN-3AJ | pancreatic gamma-glutamyltransferase Human mRNA for 2031 | 1673C>T | S558L |

|        |        |        |         |                                                                             |      |         |       |
|--------|--------|--------|---------|-----------------------------------------------------------------------------|------|---------|-------|
| X60069 | X60069 | 231950 | GEN-3AJ | Human mRNA for pancreatic gamma-glutamyltransferase                         | 2047 | 1689C>T | S     |
| X60069 | X60069 | 231950 | GEN-3AJ | Human mRNA for pancreatic gamma-glutamyltransferase                         | 2147 | 1789C>T | 3     |
| X60069 | X60069 | 231950 | GEN-3AJ | Human mRNA for pancreatic gamma-glutamyltransferase                         | 2176 | 1818C>T | 3     |
| X60069 | X60069 | 231950 | GEN-3AJ | Human mRNA for pancreatic gamma-glutamyltransferase                         | 2224 | 1866C>A | 3     |
| X60957 | X60957 | 600222 | GEN-3BF | Human tie mRNA for putative receptor tyrosine kinase                        | 2194 | 2158G>A | A720T |
| X61157 | X61157 | 109635 | GEN-23  | Adrenergic receptor (Beta kinase 1-phosphorylates beta adrenergic receptor) | 203  | 96A>C   | S     |
| X61157 | X61157 | 109635 | GEN-23  | Adrenergic receptor (Beta kinase 1-phosphorylates beta adrenergic receptor) | 1372 | 1265A>G | H422R |
| X61157 | X61157 | 109635 | GEN-23  | Adrenergic receptor (Beta kinase 1-phosphorylates beta adrenergic receptor) | 1501 | 1394G>A | R465K |
| X61157 | X61157 | 109635 | GEN-23  | Adrenergic receptor (Beta kinase 1-phosphorylates beta adrenergic receptor) | 1766 | 1659C>T | S     |
| X61157 | X61157 | 109635 | GEN-23  | Adrenergic receptor (Beta kinase 1-phosphorylates beta adrenergic receptor) | 1823 | 1716T>C | S     |
| X61157 | X61157 | 109635 | GEN-23  | Adrenergic receptor (Beta kinase 1-phosphorylates beta adrenergic receptor) | 2976 | 2869G>A | 3     |
| NFKB2  | X61498 | 164012 | GEN-3BW | Adrenergic receptor (Beta kinase 1-phosphorylates beta adrenergic receptor) | 2457 | 2294C>T | P765L |
| KDR    | X61656 | 191306 | GEN-3BZ | H.sapiens mRNA for NF-kB subunit                                            | 2308 | 2308A>G | T770A |
| KDR    | X61656 | 191306 | GEN-3BZ | H.sapiens mRNA for growth factor receptor tyrosine kinase                   | 2353 | 2353G>C | G785R |



|        |        |        |         |                                                                |         |       |
|--------|--------|--------|---------|----------------------------------------------------------------|---------|-------|
| KDR    | X61656 | 191306 | GEN-3BZ | H.sapiens mRNA for growth factor receptor tyrosine kinase      | 2499C>G | N833K |
| KDR    | X61656 | 191306 | GEN-3BZ | H.sapiens mRNA for growth factor receptor tyrosine kinase      | 2537A>T | E846V |
| KDR    | X61656 | 191306 | GEN-3BZ | H.sapiens mRNA for growth factor receptor tyrosine kinase      | 4123G>C | 3     |
| X63359 | X63359 | 600070 | GEN-3DC | H.sapiens UGT2B10 mRNA for udp glucuronosyltransferase         | 1506C>T | S     |
| X63359 | X63359 | 600070 | GEN-3DC | H.sapiens UGT2B10 mRNA for udp glucuronosyltransferase         | 2704G>A | 3     |
| ACLY   | X64330 | 108728 | GEN-3F0 | H.sapiens mRNA for ATP-citrate lyase                           | 3914G>T | 3     |
| ACLY   | X64330 | 108728 | GEN-3F0 | H.sapiens mRNA for ATP-citrate lyase                           | 4145A>C | 3     |
| X65019 | X65019 | 147678 | GEN-6G  | INTERLEUKIN 1 BETA 51 CONVERTASE PRECURSOR                     | 44G>A   | R15H  |
| X65019 | X65019 | 147678 | GEN-6G  | INTERLEUKIN 1 BETA 116 CONVERTASE PRECURSOR                    | 109A>C  | K37Q  |
| X65019 | X65019 | 147678 | GEN-6G  | INTERLEUKIN 1 BETA 261 CONVERTASE PRECURSOR                    | 254G>A  | G85E  |
| X66364 | X66364 | 123831 | GEN-3GM | H.sapiens mRNA for PSSALRE for serine/threonine protein kinase | 471T>G  | C157W |
| X66403 | X66403 | 100725 | GEN-5D  | Nicotinic, Cholinergic receptor epsilon polypeptide            | 2225G>T | 3     |
| X66403 | X66403 | 100725 | GEN-5D  | Nicotinic, Cholinergic receptor epsilon polypeptide            | 2322A>G | 3     |
| X66403 | X66403 | 100725 | GEN-5D  | Nicotinic, Cholinergic receptor epsilon polypeptide            | 2353G>T | 3     |

|        |        |        |         |                                                                            |         |       |
|--------|--------|--------|---------|----------------------------------------------------------------------------|---------|-------|
| X69117 | X69117 | 109636 | GEN-5G  | BETA-ADRENERGIC RECEPTOR KINASE 2                                          | 1182T>C | S     |
| X69117 | X69117 | 109636 | GEN-5G  | BETA-ADRENERGIC RECEPTOR KINASE 2                                          | 1609G>A | E537K |
| X69141 | X69141 | 184420 | GEN-3J9 | H.sapiens mRNA for squalene synthase                                       | 21T>C   | S     |
| X69141 | X69141 | 184420 | GEN-3J9 | H.sapiens mRNA for squalene synthase                                       | 201C>T  | S     |
| X69141 | X69141 | 184420 | GEN-3J9 | H.sapiens mRNA for squalene synthase                                       | 1345T>C | 3     |
| X69141 | X69141 | 184420 | GEN-3J9 | H.sapiens mRNA for squalene synthase                                       | 1488T>C | 3     |
| X69141 | X69141 | 184420 | GEN-3J9 | H.sapiens mRNA for squalene synthase                                       | 1530C>T | 3     |
| X69141 | X69141 | 184420 | GEN-3J9 | H.sapiens mRNA for squalene synthase                                       | 1628A>C | 3     |
| X69141 | X69141 | 184420 | GEN-3J9 | H.sapiens mRNA for squalene synthase                                       | 1813G>C | 3     |
| X70811 | X70811 | 109691 | GEN-3KK | beta-3-adrenergic receptor                                                 | 190T>C  | W64R  |
| X70811 | X70811 | 109691 | GEN-3KK | beta-3-adrenergic receptor                                                 | 190T>C  | W64R  |
| X71440 | X71440 | None   | GEN-3KS | H.sapiens mRNA for peroxisomal acyl-CoA oxidase                            | 936G>C  | M312I |
| GPX4   | X71973 | 138322 | GEN-3L1 | H.sapiens GPx-4 mRNA for phospholipid hydroperoxide glutathione peroxidase | 638T>C  | 3     |
| GPX4   | X71973 | 138322 | GEN-3L1 | H.sapiens GPx-4 mRNA for phospholipid hydroperoxide glutathione peroxidase | 757C>A  | 3     |
| GPX4   | X71973 | 138322 | GEN-3L1 | H.sapiens GPx-4 mRNA for phospholipid hydroperoxide glutathione peroxidase | 802A>C  | 3     |
| NOS2A  | X73029 | 163730 | GEN-3LW | H.sapiens mRNA for nitric oxide synthase                                   | 1155C>T | S     |
| NOS2A  | X73029 | 163730 | GEN-3LW | H.sapiens mRNA for nitric oxide synthase                                   | 1278C>T | S     |

|        |        |        |             |                                                                            |      |         |       |
|--------|--------|--------|-------------|----------------------------------------------------------------------------|------|---------|-------|
| NOS2A  | X73029 | 163730 | GEN-<br>3LW | H.sapiens mRNA for nitric<br>oxide synthase                                | 2048 | 1823C>T | S608L |
| NOS2A  | X73029 | 163730 | GEN-<br>3LW | H.sapiens mRNA for nitric<br>oxide synthase                                | 2287 | 2062G>A | G688S |
| NOS2A  | X73029 | 163730 | GEN-<br>3LW | H.sapiens mRNA for nitric<br>oxide synthase                                | 2339 | 2114A>G | D705G |
| NOS2A  | X73029 | 163730 | GEN-<br>3LW | H.sapiens mRNA for nitric<br>oxide synthase                                | 2583 | 2358T>C | S     |
| NOS2A  | X73029 | 163730 | GEN-<br>3LW | H.sapiens mRNA for nitric<br>oxide synthase                                | 2982 | 2757A>G | S     |
| NOS2A  | X73029 | 163730 | GEN-<br>3LW | H.sapiens mRNA for nitric<br>oxide synthase                                | 3022 | 2797C>G | R933G |
| NOS2A  | X73029 | 163730 | GEN-<br>3LW | H.sapiens mRNA for nitric<br>oxide synthase                                | 3051 | 2826C>T | S     |
| NOS2A  | X73029 | 163730 | GEN-<br>3LW | H.sapiens mRNA for nitric<br>oxide synthase                                | 3693 | 3468T>C | 3     |
| NOS2A  | X73029 | 163730 | GEN-<br>3LW | H.sapiens mRNA for nitric<br>oxide synthase                                | 3715 | 3490G>A | 3     |
| PREP   | X74496 | 600400 | GEN-<br>3N8 | Prolyl Endopeptidase                                                       | 390  | 390T>C  | S     |
| PREP   | X74496 | 600400 | GEN-<br>3N8 | Prolyl Endopeptidase                                                       | 1051 | 1051T>G | L351V |
| PREP   | X74496 | 600400 | GEN-<br>3N8 | Prolyl Endopeptidase                                                       | 1125 | 1125C>T | S     |
| PREP   | X74496 | 600400 | GEN-<br>3N8 | Prolyl Endopeptidase                                                       | 1363 | 1363G>A | V455M |
| X75299 | X75299 | 192321 | GEN-<br>3NU | H.sapiens HIVR mRNA for<br>vasoactive intestinal<br>peptide (VIP) receptor | 1915 | 1904T>C | 3     |
| X75299 | X75299 | 192321 | GEN-<br>3NU | H.sapiens HIVR mRNA for<br>vasoactive intestinal<br>peptide (VIP) receptor | 2475 | 2464T>C | 3     |
| MTP    | X75500 | 157147 | GEN-<br>3O7 | H.sapiens mRNA for<br>microsomal triglyceride<br>transfer protein          | 1847 | 1823T>G | F608C |
| MTP    | X75500 | 157147 | GEN-<br>3O7 | H.sapiens mRNA for<br>microsomal triglyceride<br>transfer protein          | 3231 | 3207G>A | 3     |
| X75913 | X75913 | 601269 | GEN-<br>3OG | H.sapiens mRNA for gC1q-<br>R                                              | 1052 | 974A>G  | 3     |
| X75913 | X75913 | 601269 | GEN-        | H.sapiens mRNA for gC1q-                                                   | 1074 | 996T>C  | 3     |

|        |        | 3OG    | R       |                                                                                                                                    |               |
|--------|--------|--------|---------|------------------------------------------------------------------------------------------------------------------------------------|---------------|
| X76180 | X76180 | 600228 | GEN-N5  | Solute carrier family 9 (sodium/hydrogen exchanger), isoform 1 (antiporter, Na <sup>+</sup> /H <sup>+</sup> , amiloride sensitive) | 1802G>A G601D |
|        | LIPA   | X76488 | 278000  | H.sapiens mRNA for lysosomal acid lipase                                                                                           | 46A>C T16P    |
|        | LIPA   | X76488 | 278000  | H.sapiens mRNA for lysosomal acid lipase                                                                                           | 67G>A G23R    |
|        | LIPA   | X76488 | 278000  | H.sapiens mRNA for lysosomal acid lipase                                                                                           | 822G>A M274I  |
|        | LIPA   | X76488 | 278000  | H.sapiens mRNA for lysosomal acid lipase                                                                                           | 1386C>T 3     |
|        | LIPA   | X76488 | 278000  | H.sapiens mRNA for lysosomal acid lipase                                                                                           | 2109A>T 3     |
|        | LIPA   | X76488 | 278000  | H.sapiens mRNA for lysosomal acid lipase                                                                                           | 2294C>T 3     |
| X77094 | X77094 | 601488 | GEN-3P2 | H.sapiens mRNA for p40phox                                                                                                         | 735C>T S      |
| YWHAH  | X78138 | 113508 | GEN-3QU | H.sapiens 14-3-3 eta subtype mRNA                                                                                                  | 753A>G 3      |
| YWHAH  | X78138 | 113508 | GEN-3QU | H.sapiens 14-3-3 eta subtype mRNA                                                                                                  | 760G>A 3      |
| YWHAH  | X78138 | 113508 | GEN-3QU | H.sapiens 14-3-3 eta subtype mRNA                                                                                                  | 1187C>T 3     |
| X78282 | X78282 | 601292 | GEN-LVF | H.sapiens mRNA for aryl sulfotransferase (ST1A2)                                                                                   | 895T>C 3      |
| X78706 | X78706 | 600184 | GEN-2A  | Carnitine Acetyltransferase                                                                                                        | 1922G>A 3     |
| X78706 | X78706 | 600184 | GEN-2A  | Carnitine Acetyltransferase                                                                                                        | 2378G>A 3     |
| X78706 | X78706 | 600184 | GEN-2A  | Carnitine Acetyltransferase                                                                                                        | 2382G>A 3     |
| X79483 | X79483 | 602399 | GEN-LPR | H.sapiens ERK6 mRNA for extracellular signal regulated kinase                                                                      | 1254T>G 3     |
| TNNT2  | X79857 | 191045 | GEN-3TJ | H.sapiens HTNT4 mRNA for cardiac troponin T                                                                                        | 80G>T W27L    |
| TNNT2  | X79857 | 191045 | GEN-3TJ | H.sapiens HTNT4 mRNA for cardiac troponin T                                                                                        | 114G>C S      |
| TNNT2  | X79857 | 191045 | GEN-3TJ | H.sapiens HTNT4 mRNA for cardiac troponin T                                                                                        | 193G>T F      |

|        |        |        |         |                                                                                     |           |       |
|--------|--------|--------|---------|-------------------------------------------------------------------------------------|-----------|-------|
| TNNT2  | X79857 | 191045 | GEN-3TJ | H.sapiens HTNT4 mRNA 920<br>for cardiac troponin T                                  | 809C>A    | 3     |
| X80230 | X80230 | 603251 | GEN-3UM | H.sapiens mRNA (clone C- 25<br>2k) mRNA for<br>serine/threonine protein<br>kinase   | (-74)C>T  | 5     |
| X80230 | X80230 | 603251 | GEN-3UM | H.sapiens mRNA (clone C- 77<br>2k) mRNA for<br>serine/threonine protein<br>kinase   | (-22)C>T  | 5     |
| X80230 | X80230 | 603251 | GEN-3UM | H.sapiens mRNA (clone C- 1516<br>2k) mRNA for<br>serine/threonine protein<br>kinase | 1418G>A   | 3     |
| X80230 | X80230 | 603251 | GEN-3UM | H.sapiens mRNA (clone C- 1574<br>2k) mRNA for<br>serine/threonine protein<br>kinase | 1476A>G   | 3     |
| X81411 | X81411 | None   | GEN-4EY | Serotonin 5-HT receptors 75<br>5-HT5a                                               | 76A>T     | 3     |
| X83582 | X83582 | 600734 | GEN-3YD | Potassium channel Kir3.4 171                                                        | 171C>T    | S     |
| X83582 | X83582 | 600734 | GEN-3YD | Potassium channel Kir3.4 834                                                        | 834C>T    | S     |
| X83861 | X83861 | 176806 | GEN-5H  | Prostaglandin E receptor 3 387<br>(subtype EP3) {alternative<br>products}           | 180C>G    | S     |
| X84213 | X84213 | 600516 | GEN-3ZC | H.sapiens BAK mRNA for 32<br>BCI-2 homologue                                        | (-161)C>T | 5     |
| X84213 | X84213 | 600516 | GEN-3ZC | H.sapiens BAK mRNA for 317<br>BCI-2 homologue                                       | 125G>A    | R42H  |
| X84213 | X84213 | 600516 | GEN-3ZC | H.sapiens BAK mRNA for 435<br>BCI-2 homologue                                       | 243C>T    | S     |
| X84213 | X84213 | 600516 | GEN-3ZC | H.sapiens BAK mRNA for 616<br>BCI-2 homologue                                       | 424G>A    | V142I |
| X84213 | X84213 | 600516 | GEN-3ZC | H.sapiens BAK mRNA for 663<br>BCI-2 homologue                                       | 471C>T    | S     |
| X84213 | X84213 | 600516 | GEN-3ZC | H.sapiens BAK mRNA for 900<br>BCI-2 homologue                                       | 708T>C    | 3     |
| X84213 | X84213 | 600516 | GEN-3ZC | H.sapiens BAK mRNA for 974<br>BCI-2 homologue                                       | 782C>T    | 3     |

|        |        |        |         |                                                      |       |           |        |
|--------|--------|--------|---------|------------------------------------------------------|-------|-----------|--------|
| X86097 | X86097 | 600967 | GEN-400 | H.sapiens mRNA for E2F-5 protein                     | 162   | 132G>C    | S      |
| X86097 | X86097 | 600967 | GEN-400 | H.sapiens mRNA for E2F-5 protein                     | 1281  | 1251T>C   | 3      |
| X86097 | X86097 | 600967 | GEN-400 | H.sapiens mRNA for E2F-5 protein                     | 1725  | 1695A>C   | 3      |
| X86681 | X86681 | 602110 | GEN-41E | H.sapiens mRNA for nucleolar protein, HNP36          | 1725  | 1340G>A   | 3      |
| X93086 | X93086 | 109750 | GEN-48G | H.sapiens mRNA for biliverdin IX alpha reductase     | 669   | 609G>A    | S      |
| X93086 | X93086 | 109750 | GEN-48G | H.sapiens mRNA for biliverdin IX alpha reductase     | 720   | 660A>G    | S      |
| X95190 | X95190 | 601641 | GEN-49Y | H.sapiens mRNA for Branched chain Acyl-CoA Oxidase   | 1394  | 1302C>T   | S      |
| X95190 | X95190 | 601641 | GEN-49Y | H.sapiens mRNA for Branched chain Acyl-CoA Oxidase   | 1934  | 1842C>A   | S      |
| X97058 | X97058 | 602451 | GEN-48B | P2 purinoceptor (P2Y6)                               | 121   | (-156)T>G | 5      |
| R9R2   | X98330 | 180902 | GEN-4CB | H.sapiens mRNA for ryanodine receptor 2              | 13745 | 13624G>A  | A4542T |
| R9R2   | X98330 | 180902 | GEN-4CB | H.sapiens mRNA for ryanodine receptor 2              | 15541 | 15420T>G  | 3      |
| Y00285 | Y00285 | 147280 | GEN-6I  | IGF-2 receptor                                       | 4613  | 4466G>A   | S1489N |
| Y00285 | Y00285 | 147280 | GEN-6I  | IGF-2 receptor                                       | 6371  | 6224C>T   | T2075M |
| Y00285 | Y00285 | 147280 | GEN-6I  | IGF-2 receptor                                       | 6813  | 6666C>T   | S      |
| Y00285 | Y00285 | 147280 | GEN-6I  | IGF-2 receptor                                       | 7150  | 7003G>A   | V2335M |
| Y00285 | Y00285 | 147280 | GEN-6I  | IGF-2 receptor                                       | 8685  | 8538C>A   | 3      |
| GPX1   | Y00433 | 138320 | GEN-TJ  | Human mRNA for glutathione peroxidase (EC 1.11.1.9.) | 504   | 186G>A    | S      |
| GPX1   | Y00433 | 138320 | GEN-TJ  | Human mRNA for glutathione peroxidase (EC 1.11.1.9.) | 610   | 292C>G    | R98G   |
| GPX1   | Y00433 | 138320 | GEN-TJ  | Human mRNA for glutathione peroxidase (EC 1.11.1.9.) | 911   | 593C>T    | P198L  |

|        |        |        |             |                                                                                      |         |        |
|--------|--------|--------|-------------|--------------------------------------------------------------------------------------|---------|--------|
| GPX1   | Y00433 | 138320 | GEN-TJ      | Human mRNA for 1048<br>glutathione peroxidase (EC<br>1.11.1.9.)                      | 730A>C  | 3      |
| GPX1   | Y00433 | 138320 | GEN-TJ      | Human mRNA for 1110<br>glutathione peroxidase (EC<br>1.11.1.9.)                      | 792A>C  | 3      |
| ALAS1  | Y00451 | 125290 | GEN-TE      | Human mRNA for 5-<br>aminolevulinate synthase                                        | 426T>G  | S      |
| ALAS1  | Y00451 | 125290 | GEN-TE      | Human mRNA for 5-<br>aminolevulinate synthase                                        | 525C>T  | S      |
| PAI2   | Y00630 | 173390 | GEN-U6      | Human mRNA for Arg-<br>Serpine (plasminogen<br>activator-inhibitor 2, PAI-2)         | 358A>G  | N120D  |
| PAI2   | Y00630 | 173390 | GEN-U6      | Human mRNA for Arg-<br>Serpine (plasminogen<br>activator-inhibitor 2, PAI-2)         | 1179T>G | S      |
| PAI2   | Y00630 | 173390 | GEN-U6      | Human mRNA for Arg-<br>Serpine (plasminogen<br>activator-inhibitor 2, PAI-2)         | 1690G>A | 3      |
| Y00692 | Y00692 | 176880 | GEN-6K      | Anticoagulant protein S 785                                                          | 586C>T  | 3      |
| Y00692 | Y00692 | 176880 | GEN-6K      | Anticoagulant protein S 910                                                          | 711T>C  | 3      |
| Y00692 | Y00692 | 176880 | GEN-6K      | Anticoagulant protein S 1156                                                         | 957G>T  | 3      |
| Y00749 | Y00749 | 131240 | GEN-P7      | Endothelin 1 846                                                                     | 594G>T  | K198N  |
| CR1    | Y00816 | 120620 | GEN-UG      | Human mRNA for 207<br>complement receptor type<br>1 (CR1, C3b/C4b receptor,<br>CD35) | 180G>C  | E60D   |
| Y07683 | Y07683 | 600843 | GEN-<br>4F1 | H. sapiens mRNA for P2X3 717<br>purinoceptor                                         | 552C>T  | S      |
| Y07683 | Y07683 | 600843 | GEN-<br>4F1 | H. sapiens mRNA for P2X3 753<br>purinoceptor                                         | 588A>G  | S      |
| Y08110 | Y08110 | 602005 | GEN-<br>1FK | H. sapiens mRNA for 3641<br>mosaic protein LR11                                      | 3561T>G | S      |
| Y08110 | Y08110 | 602005 | GEN-<br>1FK | H. sapiens mRNA for 3818<br>mosaic protein LR11                                      | 3738C>T | S      |
| Y08110 | Y08110 | 602005 | GEN-<br>1FK | H. sapiens mRNA for 5158<br>mosaic protein LR11                                      | 5078G>A | S1693N |
| Y08110 | Y08110 | 602005 | GEN-<br>1FK | H. sapiens mRNA for 6571<br>mosaic protein LR11                                      | 6491G>A | R2164K |
| Y08756 | Y08756 | 602164 | GEN-<br>4EC | Serotonin 5-HT receptors 765<br>5-HT4                                                | 747T>C  | S      |

|        |        |        |         |                                                     |      |         |       |
|--------|--------|--------|---------|-----------------------------------------------------|------|---------|-------|
| Y09561 | Y09561 | None   | GEN-4F4 | H.sapiens mRNA for P2X7 receptor                    | 835  | 809A>G  | H270R |
| Y09561 | Y09561 | None   | GEN-4F4 | H.sapiens mRNA for P2X7 receptor                    | 946  | 920G>A  | R307Q |
| Y09561 | Y09561 | None   | GEN-4F4 | H.sapiens mRNA for P2X7 receptor                    | 1068 | 1042G>A | A348T |
| Y09561 | Y09561 | None   | GEN-4F4 | H.sapiens mRNA for P2X7 receptor                    | 1096 | 1070C>G | T357S |
| Y09561 | Y09561 | None   | GEN-4F4 | H.sapiens mRNA for P2X7 receptor                    | 1405 | 1379A>G | Q460R |
| Y09561 | Y09561 | None   | GEN-4F4 | H.sapiens mRNA for P2X7 receptor                    | 1589 | 1563C>G | H521Q |
| Y09561 | Y09561 | None   | GEN-4F4 | H.sapiens mRNA for P2X7 receptor                    | 1590 | 1564G>A | V522I |
| Y09561 | Y09561 | None   | GEN-4F4 | H.sapiens mRNA for P2X7 receptor                    | 1628 | 1602G>T | S     |
| Y09561 | Y09561 | None   | GEN-4F4 | H.sapiens mRNA for P2X7 receptor                    | 1759 | 1733G>A | R578Q |
| Y09561 | Y09561 | None   | GEN-4F4 | H.sapiens mRNA for P2X7 receptor                    | 1772 | 1746G>A | S     |
| Y10659 | Y10659 | 300119 | GEN-1J6 | H.sapiens IL-13Ra mRNA                              | 1116 | 1073G>A | G358D |
| IREB1  | Z11559 | 147581 | GEN-1KO | H.sapiens mRNA for iron regulatory factor           | 2855 | 2748T>C | 3     |
| IREB1  | Z11559 | 147581 | GEN-1KO | H.sapiens mRNA for iron regulatory factor           | 3162 | 3055C>A | 3     |
| IREB1  | Z11559 | 147581 | GEN-1KO | H.sapiens mRNA for iron regulatory factor           | 3460 | 3353A>T | 3     |
| Z11695 | Z11695 | 176948 | GEN-1L1 | H.sapiens 40 kDa protein kinase related to rat ERK2 | 1287 | 1153G>A | 3     |
| Z11696 | Z11696 | 601795 | GEN-1L0 | H.sapiens 44kDa protein kinase related to rat ERK1  | 449  | 449T>G  | I150S |
| Z15108 | Z15108 | 176982 | GEN-1TE | H.sapiens mRNA for protein kinase C zeta            | 246  | 240T>C  | S     |
| Z15108 | Z15108 | 176982 | GEN-1TE | H.sapiens mRNA for protein kinase C zeta            | 1694 | 1688A>C | D563A |
| Z15108 | Z15108 | 176982 | GEN-1TE | H.sapiens mRNA for protein kinase C zeta            | 2033 | 2027G>A | 3     |
| Z15108 | Z15108 | 176982 | GEN-1TE | H.sapiens mRNA for protein kinase C zeta            | 2086 | 2080T>G | 3     |
| Z19585 | Z19585 | 600715 | GEN-22A | H.sapiens mRNA for thrombospondin-4                 | 2135 | 2108G>A | C703Y |



|        |        |        |         |                                                      |      |         |       |
|--------|--------|--------|---------|------------------------------------------------------|------|---------|-------|
| Z22555 | Z22555 | 601040 | GEN-264 | H.sapiens encoding CLA-1 mRNA                        | 1119 | 1050C>T | S     |
| Z22555 | Z22555 | 601040 | GEN-264 | H.sapiens encoding CLA-1 mRNA                        | 2553 | 2484A>G | 3     |
| TPM1   | Z24727 | 191010 | GEN-280 | H.sapiens tropomyosin isoform mRNA, complete CDS     | 585  | 259G>T  | F     |
| TPM1   | Z24727 | 191010 | GEN-280 | H.sapiens tropomyosin isoform mRNA, complete CDS     | 606  | 280G>T  | F     |
| TPM1   | Z24727 | 191010 | GEN-280 | H.sapiens tropomyosin isoform mRNA, complete CDS     | 668  | 342C>A  | S     |
| TPM1   | Z24727 | 191010 | GEN-280 | H.sapiens tropomyosin isoform mRNA, complete CDS     | 780  | 454C>A  | Q152K |
| TPM1   | Z24727 | 191010 | GEN-280 | H.sapiens tropomyosin isoform mRNA, complete CDS     | 1333 | 1007T>C | 3     |
| TPM1   | Z24727 | 191010 | GEN-280 | H.sapiens tropomyosin isoform mRNA, complete CDS     | 1356 | 1030A>G | 3     |
| TPM1   | Z24727 | 191010 | GEN-280 | H.sapiens tropomyosin isoform mRNA, complete CDS     | 1553 | 1227T>G | 3     |
| Z26649 | Z26649 | 600230 | GEN-2B5 | Phospholipase C beta-3                               | 437  | 438C>T  | 3     |
| Z26649 | Z26649 | 600230 | GEN-2B5 | Phospholipase C beta-3                               | 466  | 467G>A  | 3     |
| Z26649 | Z26649 | 600230 | GEN-2B5 | Phospholipase C beta-3                               | 2664 | 2665C>T | 3     |
| Z26649 | Z26649 | 600230 | GEN-2B5 | Phospholipase C beta-3                               | 3168 | 3169G>T | 3     |
| CPO    | Z28409 | 121300 | GEN-2D8 | H.sapiens coprox gene for coproporphyrinogen oxidase | 1994 | 1994G>A | 3     |
| ECE1   | Z35307 | 600423 | GEN-2MA | Endothelin Converting Enzyme 1                       | 1141 | 1104C>T | S     |
| ECE1   | Z35307 | 600423 | GEN-2MA | Endothelin Converting Enzyme 1                       | 1627 | 1590T>C | S     |
| ECE1   | Z35307 | 600423 | GEN-2MA | Endothelin Converting Enzyme 1                       | 1696 | 1659G>A | S     |

|        |        |        |      |                                            |         |       |
|--------|--------|--------|------|--------------------------------------------|---------|-------|
| ECE1   | Z35307 | 600423 | 2MA  | Enzyme 1                                   | 1909G>A | V637M |
|        | GEN-   |        | GEN- | Endothelin Converting                      |         |       |
| ECE1   | Z35307 | 600423 | 2MA  | Enzyme 1                                   | 2396G>A | 3     |
|        | GEN-   |        | GEN- | Endothelin Converting                      |         |       |
| Z35491 | Z35491 | 601497 | 2MA  | Enzyme 1                                   | 37G>A   | E13K  |
|        | GEN-   |        | GEN- | H.sapiens mRNA for novel                   |         |       |
|        | 2ME    |        | 2ME  | glucocorticoid receptor-associated protein |         |       |
| Z35491 | Z35491 | 601497 | GEN- | H.sapiens mRNA for novel                   | 55G>A   | E19K  |
|        | 2ME    |        | 2ME  | glucocorticoid receptor-associated protein |         |       |
| Z35491 | Z35491 | 601497 | GEN- | H.sapiens mRNA for novel                   | 1019A>C | 3     |
|        | 2ME    |        | 2ME  | glucocorticoid receptor-associated protein |         |       |
| Z48810 | Z48810 | 602664 | GEN- | H.sapiens mRNA for TX                      | 1239A>C | 3     |
|        | 2YJ    |        | 2YJ  | protease precursor                         |         |       |
| Z69881 | Z69881 | 601929 | GEN- | H.sapiens mRNA for                         | 2017G>A | A673T |
|        | 3JV    |        | 3JV  | adenosine triphosphatase, calcium          |         |       |
| Z69881 | Z69881 | 601929 | GEN- | H.sapiens mRNA for                         | 3630C>G | 3     |
|        | 3JV    |        | 3JV  | adenosine triphosphatase, calcium          |         |       |

Table 18. Identified  
Variances in Genes or  
Related Pathways  
involved in Cancer and  
Related Disorders

|                                                    |        |        |                                    |
|----------------------------------------------------|--------|--------|------------------------------------|
| human DNA mismatch<br>repair protein<br>hMLH1/MutL | U07418 | 120436 | SER252TER                          |
| human DNA mismatch<br>repair protein<br>hMLH1/MutL | U07418 | 120436 | SER44PHE                           |
| human DNA mismatch<br>repair protein<br>hMLH1/MutL | U07418 | 120436 | 3-BP DEL LYS618DEL                 |
| human DNA mismatch<br>repair protein<br>hMLH1/MutL | U07418 | 120436 | 3.5-KB DEL                         |
| human DNA mismatch<br>repair protein<br>hMLH1/MutL | U07418 | 120436 | G-to-A intron 5<br>splice junction |
| human DNA mismatch<br>repair protein<br>hMLH1/MutL | U07418 | 120436 | 370-BP DEL frameshift              |
| human DNA mismatch<br>repair protein<br>hMLH1/MutL | U07418 | 120436 | IVS14DS, 7-BP<br>DEL AND 4-BP INS  |
| human DNA mismatch<br>repair protein<br>hMLH1/MutL | U07418 | 120436 | HIS329PRO                          |
| human DNA mismatch                                 | U07418 | 120436 | 1784delT truncated                 |

|                                                    |        |        |                                          |
|----------------------------------------------------|--------|--------|------------------------------------------|
| repair protein<br>hMLH1/MutL                       | U07418 | 120436 | 676C-T ARG226TER                         |
| human DNA mismatch<br>repair protein<br>hMLH1/MutL | U07418 | 120436 | GGG to TGG GLY67TRP                      |
| human DNA mismatch<br>repair protein<br>hMLH1/MutL | U07418 | 120436 | A-->T codon 26                           |
| human DNA mismatch<br>repair protein<br>hMLH1/MutL | U07418 | 120436 | GG-->AT 177 and 178                      |
| human DNA mismatch<br>repair protein<br>hMLH1/MutL | U07418 | 120436 | -93 nt                                   |
| human DNA mismatch<br>repair protein<br>hMLH1/MutL | U07418 | 120436 | Val384Asp                                |
| human DNA mismatch<br>repair protein<br>hMLH1/MutL | U07418 | 120436 | T insertion 3 splice<br>site post exon 9 |
| human DNA mismatch<br>repair protein<br>hMLH1/MutL | U07418 | 120436 | deletion of<br>codon 618K                |
| human DNA mismatch<br>repair protein<br>hMLH1/MutL | U07418 | 120436 | A-to-G transition<br>exon 6              |
| human DNA mismatch<br>repair protein<br>hMLH1/MutL | U07418 | 120436 | exon 5 missense                          |

|                                                    |          |        |                       |
|----------------------------------------------------|----------|--------|-----------------------|
| hMLH1/MutL<br>human DNA mismatch<br>repair protein | U07418   | 120436 | exon 9 missense       |
| hMLH1/MutL<br>topoisomerase IIb                    | U54831   | 126431 | reported              |
| O6 alkylguanine-DNA<br>alkyltransferase            | M60761   | 156569 | GGA to AGA GLY160ARG  |
| class I aldehyde<br>dehydrogenase                  | M26761   | 100640 | none found            |
| glutathione-S-<br>transferase GSTA4                | AF020918 | *****  | none found            |
| glutathione-S-<br>transferase GSTM3                | J05459   | 138390 | 3bp deletion intron 6 |
| glutathione-S-<br>transferase GSTT1                | X79389   | 600436 | null genotype         |
| glutathione-S-<br>transferase GSTT2                | L38503   | 600437 | none found            |
| glutathione peroxidase<br>GPx1                     | Y00433   | 138320 | P197L                 |
| glutathione peroxidase<br>GPx1                     | Y00433   | 138320 | 1167T/C Silent        |
| glutathione peroxidase<br>GPx2                     | X68314   | 138319 | A/T intron            |
| glutathione peroxidase<br>GPx2                     | X68314   | 138319 | TC repeats intron     |
| glutathione peroxidase<br>GPx3                     | X58295   | 138321 | none found            |
| glutathione peroxidase<br>GPx4                     | X71973   | 138322 | none found            |
| glutathione peroxidase<br>GPx5                     | AJ005277 | 603435 | none found            |

|                                         |        |        |                            |
|-----------------------------------------|--------|--------|----------------------------|
| glutathione reductase                   | X15722 | 138300 | two polymorphisms reported |
| N-methylpurine-DNA glycosylase          | M74905 | 156565 | none found                 |
| proliferating cell nuclear antigen      | J04718 | 176740 | none found                 |
| multidrug resistance associated protein | L05628 | 158343 | none found                 |
| MRP1                                    |        |        |                            |
| multidrug resistance associated protein | U83659 | 601107 | none found                 |
| MRP2                                    |        |        |                            |
| dihydrofolate reductase                 | J00140 | 126060 | intronic polymorphism      |
| dihydrofolate reductase                 | J00140 | 126060 | 2 RFLP's                   |
| thymidylate synthetase                  | X02308 | 188350 | 5' trinucleotide repeat    |
| thymidylate synthetase                  | X02308 | 188350 | tyr33his                   |
| thymidylate synthetase                  | X02308 | 188350 | A->G 3'UTR                 |
| human cell adhesion protein SQM1        | M33374 | 603842 | none found                 |
| reduced folate carrier                  | U19720 | 600424 | none found                 |
| RFC1                                    |        |        |                            |
| thymidylate synthetase                  | X02308 | 188350 | Triple tandem 5'end        |
| thymidylate synthetase                  | X02308 | 188350 | tyr33his                   |
| cytidine deaminase                      | L27943 | 123920 | none found                 |
| folypolyglutamate synthetase FPGS       | M98045 | 136510 | none found                 |
| gamma-glutamyl hydrolase GGH            | U55206 | 601509 | none found                 |
| dihydropyrimidine                       | U09178 | 274270 | 165-BP DEL                 |

|                              |        |        |                                     |
|------------------------------|--------|--------|-------------------------------------|
| dehydrogenase DPD            | U09178 | 274270 | ASP974VAL                           |
| dihydropyrimidine            |        |        |                                     |
| dehydrogenase DPD            | U09178 | 274270 | 4-BP DEL 296 to<br>299 (TCAT)       |
| dihydropyrimidine            |        |        |                                     |
| dehydrogenase DPD            | U09178 | 274270 | CYS29ARG                            |
| dihydropyrimidine            |        |        |                                     |
| dehydrogenase DPD            | U09178 | 274270 | 1-BP DEL, 1897C Frameshift          |
| dihydropyrimidine            |        |        |                                     |
| dehydrogenase DPD            | U09178 | 274270 | ARG886HIS                           |
| dihydropyrimidine            |        |        |                                     |
| dehydrogenase DPD            | U09178 | 274270 | Arg21Gln                            |
| dihydropyrimidine            |        |        |                                     |
| dehydrogenase DPD            | U09178 | 274270 | Val335Leu                           |
| dihydropyrimidine            |        |        |                                     |
| dehydrogenase DPD            | U09178 | 274270 | Glu386Ter                           |
| dihydropyrimidine            |        |        |                                     |
| dehydrogenase DPD            | U09178 | 274270 | deltaC1897                          |
| dihydropyrimidine            |        |        |                                     |
| dehydrogenase DPD            | U09178 | 274270 | Ser534Asn                           |
| dihydropyrimidine            |        |        |                                     |
| dehydrogenase DPD            | U09178 | 274270 | Ile543Val                           |
| dihydropyrimidine            |        |        |                                     |
| dehydrogenase DPD            | U09178 | 274270 | Val732Ile                           |
| dihydropyrimidine            |        |        |                                     |
| dehydrogenase DPD            | M60527 | 125450 | 115-base pair<br>deletion<br>G to A |
| deoxycytidine kinase         |        |        | glutamic acid<br>for glycine        |
| deoxycytidine kinase         | M60527 | 125450 | none found                          |
| glucosylceramide<br>synthase | D50840 | 602874 |                                     |

|                                                       |        |        |                     |
|-------------------------------------------------------|--------|--------|---------------------|
| hypoxanthine-guanine<br>phosphoribosyltransfer<br>ase | M31642 | 308000 | ILE132MET           |
| hypoxanthine-guanine<br>phosphoribosyltransfer<br>ase | M31642 | 308000 | ASP80VAL            |
| hypoxanthine-guanine<br>phosphoribosyltransfer<br>ase | M31642 | 308000 | ASP201GLY           |
| hypoxanthine-guanine<br>phosphoribosyltransfer<br>ase | M31642 | 308000 | 1-BP INS frameshift |
| hypoxanthine-guanine<br>phosphoribosyltransfer<br>ase | M31642 | 308000 | EX8DEL              |
| hypoxanthine-guanine<br>phosphoribosyltransfer<br>ase | M31642 | 308000 | LEU41PRO            |
| hypoxanthine-guanine<br>phosphoribosyltransfer<br>ase | M31642 | 308000 | 24AA+               |
| hypoxanthine-guanine<br>phosphoribosyltransfer<br>ase | M31642 | 308000 | PHE74LEU            |
| hypoxanthine-guanine<br>phosphoribosyltransfer<br>ase | M31642 | 308000 | ASP194ASN           |
| hypoxanthine-guanine<br>phosphoribosyltransfer<br>ase | M31642 | 308000 | ASP193ASN           |
| hypoxanthine-guanine<br>phosphoribosyltransfer<br>ase | M31642 | 308000 | SER110LEU           |



|                                                |        |        |           |  |
|------------------------------------------------|--------|--------|-----------|--|
| phosphoribosyltransferase                      |        |        |           |  |
| hypoxanthine-guanine phosphoribosyltransferase | M31642 | 308000 | VAL179DEL |  |
| hypoxanthine-guanine phosphoribosyltransferase | M31642 | 308000 | VAL130ASP |  |
| hypoxanthine-guanine phosphoribosyltransferase | M31642 | 308000 | ALA161SER |  |
| hypoxanthine-guanine phosphoribosyltransferase | M31642 | 308000 | SER104ARG |  |
| hypoxanthine-guanine phosphoribosyltransferase | M31642 | 308000 | PHE199VAL |  |
| hypoxanthine-guanine phosphoribosyltransferase | M31642 | 308000 | GLY70GLU  |  |
| hypoxanthine-guanine phosphoribosyltransferase | M31642 | 308000 | GLY71ARG  |  |
| hypoxanthine-guanine phosphoribosyltransferase | M31642 | 308000 | GLN108TER |  |
| hypoxanthine-guanine phosphoribosyltransferase | M31642 | 308000 | HIS203ASP |  |
| hypoxanthine-guanine phosphoribosyltransferase | M31642 | 308000 | ARG44LYS  |  |

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|                                                       |        |        |                               |
|-------------------------------------------------------|--------|--------|-------------------------------|
| ase<br>hypoxanthine-guanine<br>phosphoribosyltransfer | M31642 | 308000 | ASP176TYR                     |
| ase<br>hypoxanthine-guanine<br>phosphoribosyltransfer | M31642 | 308000 | 2-BP DEL frameshift           |
| ase<br>hypoxanthine-guanine<br>phosphoribosyltransfer | M31642 | 308000 | 1-BP DEL, TTA-TA frameshift   |
| ase<br>hypoxanthine-guanine<br>phosphoribosyltransfer | M31642 | 308000 | 1-BP DEL, TTG-TG frameshift   |
| ase<br>hypoxanthine-guanine<br>phosphoribosyltransfer | M31642 | 308000 | 40-BP DEL frameshift          |
| ase<br>hypoxanthine-guanine<br>phosphoribosyltransfer | M31642 | 308000 | G-to-A +5 intron 8 splice     |
| ase<br>hypoxanthine-guanine<br>phosphoribosyltransfer | M31642 | 308000 | ATAG-TTTG -4 intron 8+I29     |
| ase<br>hypoxanthine-guanine<br>phosphoribosyltransfer | M31642 | 308000 | GTAAGT-to-<br>GTAAAT intron 7 |
| ase<br>hypoxanthine-guanine<br>phosphoribosyltransfer | M31642 | 308000 | AG-to-TG intron 1             |
| ase<br>hypoxanthine-guanine<br>phosphoribosyltransfer | M31642 | 308000 | PRO176LEU                     |

|                                                       |        |        |                            |
|-------------------------------------------------------|--------|--------|----------------------------|
| hypoxanthine-guanine<br>phosphoribosyltransfer<br>ase | M31642 | 308000 | ARG51GLY                   |
| hypoxanthine-guanine<br>phosphoribosyltransfer<br>ase | M31642 | 308000 | ARG51TER                   |
| hypoxanthine-guanine<br>phosphoribosyltransfer<br>ase | M31642 | 308000 | MET56THR                   |
| hypoxanthine-guanine<br>phosphoribosyltransfer<br>ase | M31642 | 308000 | MET143LYS                  |
| hypoxanthine-guanine<br>phosphoribosyltransfer<br>ase | M31642 | 308000 | ARG170TER                  |
| hypoxanthine-guanine<br>phosphoribosyltransfer<br>ase | M31642 | 308000 | 13-BP DEL, 5-<br>PRIME UTR |
| hypoxanthine-guanine<br>phosphoribosyltransfer<br>ase | M31642 | 308000 | EX2DEL                     |
| hypoxanthine-guanine<br>phosphoribosyltransfer<br>ase | M31642 | 308000 | EX4-9DEL                   |
| hypoxanthine-guanine<br>phosphoribosyltransfer<br>ase | M31642 | 308000 | EX6-9DEL                   |
| hypoxanthine-guanine<br>phosphoribosyltransfer<br>ase | M31642 | 308000 | EX9DEL                     |
| hypoxanthine-guanine<br>phosphoribosyltransfer<br>ase | M31642 | 308000 | 1-BP INS G 207 frameshift  |

|                                                |        |        |                          |           |
|------------------------------------------------|--------|--------|--------------------------|-----------|
| phosphoribosyltransferase                      | M31642 | 308000 | EX2-3DUP                 |           |
| hypoxanthine-guanine phosphoribosyltransferase | M31642 | 308000 |                          | THR168ILE |
| phosphoribosyltransferase                      | M31642 | 308000 |                          | GLY16SER  |
| phosphoribosyltransferase                      | M31642 | 308000 |                          | GLY58ARG  |
| phosphoribosyltransferase                      | M31642 | 308000 |                          | LEU78VAL  |
| phosphoribosyltransferase                      | M31642 | 308000 | EX6DEL                   |           |
| phosphoribosyltransferase                      | M31642 | 308000 | 1-BP INS, T INS<br>14823 |           |
| phosphoribosyltransferase                      | M31642 | 308000 |                          | ASP52GLY  |
| phosphoribosyltransferase                      | M31642 | 308000 |                          | GLY140ASP |
| phosphoribosyltransferase                      | M31642 | 308000 |                          | ASP194GLU |

|                                                            |                            |                            |                                                                                                          |
|------------------------------------------------------------|----------------------------|----------------------------|----------------------------------------------------------------------------------------------------------|
| ase<br>hypoxanthine-guanine<br>phosphoribosyltransferase   | M31642                     | 308000                     | TYR153TER                                                                                                |
| ase<br>hypoxanthine-guanine<br>phosphoribosyltransferase   | M31642                     | 308000                     | Mnl I                                                                                                    |
| ase<br>hypoxanthine-guanine<br>phosphoribosyltransferase   | M31642                     | 308000                     | Bam HI                                                                                                   |
| ase<br>hypoxanthine-guanine<br>phosphoribosyltransferase   | M31642                     | 308000                     | 54 (from ATG<br>to CTG)<br>resulting in the<br>replacement of<br>methionine with<br>leucine<br>val179gly |
| ase<br>hypoxanthine-guanine<br>phosphoribosyltransferase   | M31642                     | 308000                     | gly180arg                                                                                                |
| ase<br>hypoxanthine-guanine<br>phosphoribosyltransferase   | M31642                     | 308000                     | 51 del 747 and 797 truncated protein                                                                     |
| Bcl-2<br>Bcl-2                                             | M13994<br>M13994           | 151430<br>151430           | ACC-->GCC Ala43Thr<br>EcoRI<br>polymorphism<br>G to A exon 2                                             |
| Bcl-2<br>protein kinase C alpha<br>protein kinase C beta 1 | M13994<br>X52479<br>X06318 | 151430<br>176960<br>176970 | ASP294GLY<br>none found                                                                                  |

|                                |           |        |                            |  |
|--------------------------------|-----------|--------|----------------------------|--|
| protein kinase C delta         | L07861    | 176977 | none found                 |  |
| protein kinase C mu            | X75756    | *****  | none found                 |  |
| protein kinase C theta         | L01087    | 600448 | none found                 |  |
| protein kinase C zeta          | L14283    | 176982 | none found                 |  |
| ecto-5'-nucleotidase<br>(CD73) | X55740    | 129190 | none found                 |  |
| alkaline phosphatase           | NM_000478 | 171760 | ALA162THR                  |  |
| alkaline phosphatase           | NM_000478 | 171760 | ARG54CYS                   |  |
| alkaline phosphatase           | NM_000478 | 171760 | ASP277ALA                  |  |
| alkaline phosphatase           | NM_000478 | 171760 | ARG54PRO                   |  |
| alkaline phosphatase           | NM_000478 | 171760 | GLN190PRO                  |  |
| alkaline phosphatase           | NM_000478 | 171760 | ALA16VAL                   |  |
| alkaline phosphatase           | NM_000478 | 171760 | TYR419HIS                  |  |
| alkaline phosphatase           | NM_000478 | 171760 | GLU174LYS                  |  |
| alkaline phosphatase           | NM_000478 | 171760 | ASP361VAL                  |  |
| alkaline phosphatase           | NM_000478 | 171760 | GLY317ASP                  |  |
| alkaline phosphatase           | NM_000478 | 171760 | PHE310LEU                  |  |
| alkaline phosphatase           | NM_000478 | 171760 | GLY439ARG                  |  |
| alkaline phosphatase           | NM_000478 | 171760 | 1-BP DEL, 1735T frameshift |  |

|                       |         |        |                               |
|-----------------------|---------|--------|-------------------------------|
| alkaline phosphatase  | NM_0004 | 171760 | ARG119HIS                     |
| 78                    |         |        |                               |
| alkaline phosphatase  | NM_0004 | 171760 | GLY145VAL                     |
| 78                    |         |        |                               |
| alkaline phosphatase  | NM_0004 | 171760 | ScrFI                         |
| 78                    |         |        |                               |
| alkaline phosphatase  | NM_0004 | 171760 | BclI                          |
| 78                    |         |        |                               |
| ribonucleotide        | X59543  | 180410 | SacI polymorphism             |
| reductase M1 subunit  |         |        | within intron IX              |
| ribonucleotide        | X59543  | 180410 | TaqI                          |
| reductase M1 subunit  |         |        |                               |
| ribonucleotide        | X59618  | 180390 | none found                    |
| reductase M2 subunit  |         |        |                               |
| aminopeptidase A      | L14721  | 138297 | none found                    |
| signal transducer and | M97935  | 600555 | none found                    |
| activator of          |         |        |                               |
| transcription STAT1   |         |        |                               |
| topoisomerase IIa     | J04088  | 126430 | AGA to AAA ARG486LYS          |
| topoisomerase IIa     | J04088  | 126430 | deletion of 1320- Deletion of |
| topoisomerase I       | J03250  | 126420 | 1322 Ala429                   |
| topoisomerase I       | J03250  | 126420 | Lys-797-->Asn                 |
| topoisomerase I       | J03250  | 126420 | Arg449Gln                     |
| topoisomerase I       | J03250  | 126420 | ASP533GLY                     |
| myeloperoxidase       | X04876  | 254600 | ASP583GLY                     |
| myeloperoxidase       | X04876  | 254600 | Asn722Ser                     |
| myeloperoxidase       | X04876  | 254600 | TaqI                          |
|                       |         |        | C8089T ARG569TRP              |
|                       |         |        | TYR173CYS                     |
|                       |         |        | MET251THR                     |

|                                            |        |        |                     |
|--------------------------------------------|--------|--------|---------------------|
| myeloperoxidase                            | X04876 | 254600 | G to A (promoter)   |
| myeloperoxidase                            | X04876 | 254600 | KpnI                |
| myeloperoxidase                            | X04876 | 254600 | Dinucleotide Repeat |
| myeloperoxidase                            | X04876 | 254600 | EcoRV               |
| myeloperoxidase                            | X04876 | 254600 | PstI                |
| b3-tubulin                                 | U47634 | 60266  | none found          |
| interleukin 6 (IL6)                        | M14584 | 147620 | 174G-C              |
| interleukin 6 (IL6)                        | M14584 | 147620 | CA repeat           |
| interleukin 6 (IL6)                        | M14584 | 147620 | NlaIII promoter     |
| interleukin 6 (IL6)                        | M14584 | 147620 | AT repeat           |
| interleukin 6 (IL6)                        | M14584 | 147620 | MspI                |
| interleukin 6 (IL6)                        | M14584 | 147620 | BglI                |
| interleukin 6 (IL6)                        | M14584 | 147620 | BglII               |
| interferon alpha1 (IFNa1)                  | X02956 | 147660 | none found          |
| tyrosine kinase-type cell surface receptor | X03363 | 164870 | VAL655ILE           |
| HER2/ERBB2                                 | X03363 | 164870 | VAL654ILE           |
| tyrosine kinase-type cell surface receptor | X02469 | 191170 | CGC-CCC Arg72 Pro   |
| HER2/ERBB2                                 | X02469 | 191170 | CCG-CTG Pro82Leu    |
| tumor protein p53                          | X02469 | 191170 | ATG-ACG Met133Thr   |
| tumor protein p53                          | X02469 | 191170 | cCAA-TAA Gln136Term |
| tumor protein p53                          | X02469 | 191170 | cAGA-TGA Arg209Term |
| tumor protein p53                          | X02469 | 191170 | aCCC-TCC Pro151Ser  |
| tumor protein p53                          | X02469 | 191170 | CCG-CTG Pro152Leu   |
| tumor protein p53                          | X02469 | 191170 | gCCC-TCC Pro219Ser  |
| tumor protein p53                          | X02469 | 191170 | cAAC-GAC Asn235Asp  |
| tumor protein p53                          | X02469 | 191170 | GGC-GTC Gly154Val   |



|                   |        |        |                     |
|-------------------|--------|--------|---------------------|
| tumor protein p53 | X02469 | 191170 | ACA-ATA Thr256Ile   |
| tumor protein p53 | X02469 | 191170 | CGC-CAC Arg175His   |
| tumor protein p53 | X02469 | 191170 | CAT-CGT His193Arg   |
| tumor protein p53 | X02469 | 191170 | tCGA-TGA Arg213Term |
| tumor protein p53 | X02469 | 191170 | gCGT-TGT Arg273Cys  |
| tumor protein p53 | X02469 | 191170 | TGT-TAT Cys275Tyr   |
| tumor protein p53 | X02469 | 191170 | tGAG-AAG Glu180Lys  |
| tumor protein p53 | X02469 | 191170 | CGC-CAC Arg181His   |
| tumor protein p53 | X02469 | 191170 | gCGC-TGC Arg181Cys  |
| tumor protein p53 | X02469 | 191170 | cCGA-TGA Arg196Term |
| tumor protein p53 | X02469 | 191170 | TAT-TGT Tyr220Cys   |
| tumor protein p53 | X02469 | 191170 | cTCT-ACT Ser227Thr  |
| tumor protein p53 | X02469 | 191170 | AAC-AGC Asn235Ser   |
| tumor protein p53 | X02469 | 191170 | CGA-CCA Arg306Pro   |
| tumor protein p53 | X02469 | 191170 | cCAC-AAC His233Asn  |
| tumor protein p53 | X02469 | 191170 | ATCc-ATG Ile251Met  |
| tumor protein p53 | X02469 | 191170 | TCC-TTC Ser241Phe   |
| tumor protein p53 | X02469 | 191170 | CGG-CAG Arg248Gln   |
| tumor protein p53 | X02469 | 191170 | GGC-GAC Gly245Asp   |
| tumor protein p53 | X02469 | 191170 | cGGC-AGC Gly245Ser  |
| tumor protein p53 | X02469 | 191170 | cCGG-TGG Arg282Trp  |
| tumor protein p53 | X02469 | 191170 | cGGC-TGC Gly245Cys  |
| tumor protein p53 | X02469 | 191170 | cCGG-TGG Arg248Trp  |
| tumor protein p53 | X02469 | 191170 | CTC-CCC Leu252Pro   |
| tumor protein p53 | X02469 | 191170 | gGAA-AAA Glu258Lys  |
| tumor protein p53 | X02469 | 191170 | CTG-CAG Leu257Gln   |
| tumor protein p53 | X02469 | 191170 | CTG-CCG Leu265Pro   |
| tumor protein p53 | X02469 | 191170 | gCGA-TGA Arg306Term |
| tumor protein p53 | X02469 | 191170 | gGTG-TTG Val272Leu  |
| tumor protein p53 | X02469 | 191170 | CGT-CAT Arg273His   |
| tumor protein p53 | X02469 | 191170 | GGA-GTA Gly325Val   |

|                                       |        |        |                             |
|---------------------------------------|--------|--------|-----------------------------|
| tumor protein p53                     | X02469 | 191170 | CCT-CTT Pro278Leu           |
| tumor protein p53                     | X02469 | 191170 | GAA-GCA Glu286Ala           |
| tumor protein p53                     | X02469 | 191170 | gCGC-TGC Arg337Cys          |
| tumor protein p53                     | X02469 | 191170 | CTG-CCG Leu344Pro           |
| tumor protein p53                     | X02469 | 191170 | ARG249SER                   |
| tumor protein p53                     | X02469 | 191170 | VAL157PHE                   |
| tumor protein p53                     | X02469 | 191170 | CYS242TYR                   |
| tumor protein p53                     | X02469 | 191170 | 1-BP INS, 151C frameshift   |
| tumor protein p53                     | X02469 | 191170 | 2-BP DEL, frameshift        |
| tumor protein p53                     | X02469 | 191170 | CODONS 209-210              |
| tumor protein p53                     | X02469 | 191170 | 1-BP INS, CODONS frameshift |
| tumor protein p53                     | X02469 | 191170 | 71-72                       |
| tumor protein p53                     | X02469 | 191170 | LYS120TER                   |
| tumor protein p53                     | X02469 | 191170 | ARG280THR                   |
| tumor protein p53                     | X02469 | 191170 | PRO151THR                   |
| tumor protein p53                     | X02469 | 191170 | LEU35PHE                    |
| tumor protein p53                     | X02469 | 191170 | 1-BP DEL, CODON             |
| tumor protein p53                     | X02469 | 191170 | 257                         |
| tumor protein p53                     | X02469 | 191170 | ALA138PRO                   |
| tumor protein p53                     | X02469 | 191170 | 1-BP DEL Codon frameshift   |
| tumor protein p53                     | X02469 | 191170 | 178                         |
| tumor necrosis factor<br>alpha (TNFa) | X01394 | 191160 | LEU29SER                    |
| tumor necrosis factor<br>alpha (TNFa) | X01394 | 191160 | -1,031 T-->C                |
| tumor necrosis factor<br>alpha (TNFa) | X01394 | 191160 | -863 C-->A                  |
| tumor necrosis factor<br>alpha (TNFa) | X01394 | 191160 | C-850T                      |
| tumor necrosis factor<br>alpha (TNFa) | X01394 | 191160 | G -238 A                    |

|                                                        |               |        |                          |          |
|--------------------------------------------------------|---------------|--------|--------------------------|----------|
| tumor necrosis factor<br>alpha (TNFa)                  | X01394        | 191160 | G-376 A                  |          |
| tumor necrosis factor<br>alpha (TNFa)                  | X01394        | 191160 | C to T, -857T            |          |
| tumor necrosis factor<br>alpha (TNFa)                  | X01394        | 191160 | -308 G/A                 |          |
| tumor necrosis factor<br>alpha (TNFa)                  | X01394        | 191160 | NcoI                     |          |
| tumor necrosis factor<br>alpha (TNFa)                  | X01394        | 191160 | C-ins 5'UTR of exon<br>1 | ARG32TRP |
| tumor necrosis factor<br>alpha (TNFa)                  | X01394        | 191160 | G-376A                   |          |
| 2',5'-oligoadenylate<br>synthetase 1 (OAS1)            | NM_0061<br>87 | 164350 | none found               |          |
| 2',5'-oligoadenylate<br>synthetase 2 (OAS2)            | M87284        | 603350 | none found               |          |
| 2',5'-oligoadenylate<br>synthetase 3 (OAS3)            | *****         | 603351 | none found               |          |
| excision repair protein<br>ERCC1                       | M13194        | 126380 | codon 118 C->T silent    |          |
| xeroderma<br>pigmentosum<br>complementation<br>group A | D14533        | 278700 | ILE132MET                |          |
| xeroderma<br>pigmentosum<br>complementation<br>group A | D14533        | 278700 | ASP80VAL                 |          |
| xeroderma                                              | D14533        | 278700 | ASP201GLY                |          |

|                                                        |        |        |                                 |           |
|--------------------------------------------------------|--------|--------|---------------------------------|-----------|
| pigmentosum<br>complementation<br>group A              | D14533 | 278700 | 56 CCTTGA to FS20TER<br>CCTTTGA |           |
| xeroderma<br>pigmentosum<br>complementation<br>group A | D14533 | 278700 | EX8DEL                          |           |
| xeroderma<br>pigmentosum<br>complementation<br>group A | D14533 | 278700 |                                 | LEU41PRO  |
| xeroderma<br>pigmentosum<br>complementation<br>group A | D14533 | 278700 |                                 | 24AA+     |
| xeroderma<br>pigmentosum<br>complementation<br>group A | D14533 | 278700 |                                 | PHE74LEU  |
| xeroderma<br>pigmentosum<br>complementation<br>group A | D14533 | 278700 |                                 | ASP194ASN |
| xeroderma<br>pigmentosum<br>complementation<br>group A | D14533 | 278700 |                                 | ASP193ASN |

|                                                        |        |        |                    |
|--------------------------------------------------------|--------|--------|--------------------|
| xeroderma<br>pigmentosum<br>complementation<br>group A | D14533 | 278700 | SER110LEU          |
| xeroderma<br>pigmentosum<br>complementation<br>group A | D14533 | 278700 | 3-BP DEL VAL179DEL |
| xeroderma<br>pigmentosum<br>complementation<br>group A | D14533 | 278700 | VAL130ASP          |
| xeroderma<br>pigmentosum<br>complementation<br>group A | D14533 | 278700 | ALA161SER          |
| xeroderma<br>pigmentosum<br>complementation<br>group A | D14533 | 278700 | SER104ARG          |
| xeroderma<br>pigmentosum<br>complementation<br>group A | D14533 | 278700 | PHE199VAL          |
| xeroderma<br>pigmentosum<br>complementation<br>group A | D14533 | 278700 | GLY70GLU           |
| xeroderma<br>pigmentosum<br>complementation<br>group A | D14533 | 278700 | GLY71ARG           |

|                                                        |        |        |                                 |
|--------------------------------------------------------|--------|--------|---------------------------------|
| group A<br>xeroderma<br>pigmentosum<br>complementation | D14533 | 278700 | GLN108TER                       |
| group A<br>xeroderma<br>pigmentosum<br>complementation | D14533 | 278700 | HIS203ASP                       |
| group A<br>xeroderma<br>pigmentosum<br>complementation | D14533 | 278700 | ARG44LYS                        |
| group A<br>xeroderma<br>pigmentosum<br>complementation | D14533 | 278700 | ASP176TYR                       |
| group A<br>xeroderma<br>pigmentosum<br>complementation | D14533 | 278700 | 2-BP DEL, GT DEL frameshift     |
| group A<br>xeroderma<br>pigmentosum<br>complementation | D14533 | 278700 | 1-BP DEL, TTA- frameshift<br>TA |
| group A<br>xeroderma<br>pigmentosum<br>complementation | D14533 | 278700 | 40-BP DEL, FS frameshift        |
| group A<br>xeroderma<br>pigmentosum                    | D14533 | 278700 | G+5A intron 8                   |

|                                                                           |        |        |                                               |           |
|---------------------------------------------------------------------------|--------|--------|-----------------------------------------------|-----------|
| complementation<br>group A<br>xeroderma<br>pigmentosum<br>complementation | D14533 | 278700 | ATAG-TTTG<br>intron 8                         |           |
| group A<br>xeroderma<br>pigmentosum<br>complementation                    | D14533 | 278700 | GTAAGT-to-<br>GTAAAT intron 7                 |           |
| group A<br>xeroderma<br>pigmentosum<br>complementation                    | D14533 | 278700 | AG-to-TG last 2<br>nucleotides of intron<br>1 | PRO176LEU |
| group A<br>xeroderma<br>pigmentosum<br>complementation                    | D14533 | 278700 |                                               | ARG51GLY  |
| group A<br>xeroderma<br>pigmentosum<br>complementation                    | D14533 | 278700 |                                               | ARG51TER  |
| group A<br>xeroderma<br>pigmentosum<br>complementation                    | D14533 | 278700 |                                               | MET56THR  |
| group A<br>xeroderma                                                      | D14533 | 278700 |                                               | MET143LYS |

|                                                        |        |        |                            |
|--------------------------------------------------------|--------|--------|----------------------------|
| pigmentosum<br>complementation<br>group A              | D14533 | 278700 | ARG170TER                  |
| xeroderma<br>pigmentosum<br>complementation<br>group A |        |        |                            |
| xeroderma<br>pigmentosum<br>complementation<br>group A | D14533 | 278700 | 13-BP DEL, 5-<br>PRIME UTR |
| xeroderma<br>pigmentosum<br>complementation<br>group A |        |        |                            |
| xeroderma<br>pigmentosum<br>complementation<br>group A | D14533 | 278700 | EX2DEL                     |
| xeroderma<br>pigmentosum<br>complementation<br>group A |        |        |                            |
| xeroderma<br>pigmentosum<br>complementation<br>group A | D14533 | 278700 | EX4-9DEL                   |
| xeroderma<br>pigmentosum<br>complementation<br>group A |        |        |                            |
| xeroderma<br>pigmentosum<br>complementation<br>group A | D14533 | 278700 | EX6-9DEL                   |
| xeroderma<br>pigmentosum<br>complementation<br>group A |        |        |                            |
| xeroderma<br>pigmentosum<br>complementation<br>group A | D14533 | 278700 | EX9DEL                     |
| xeroderma<br>pigmentosum<br>complementation<br>group A |        |        |                            |
| xeroderma<br>pigmentosum<br>complementation<br>group A | D14533 | 278700 | null allele                |
| xeroderma<br>pigmentosum<br>complementation<br>group A |        |        |                            |



|                                                        |        |        |                                                             |           |
|--------------------------------------------------------|--------|--------|-------------------------------------------------------------|-----------|
| xeroderma<br>pigmentosum<br>complementation<br>group A | D14533 | 278700 | G insertion at about<br>nucleotide 207                      |           |
| xeroderma<br>pigmentosum<br>complementation<br>group A | D14533 | 278700 | INV/DEL, EX6-9                                              |           |
| xeroderma<br>pigmentosum<br>complementation<br>group A | D14533 | 278700 | duplication of exons<br>2 and 3 and deletion<br>of intron 1 | THR168ILE |
| xeroderma<br>pigmentosum<br>complementation<br>group A | D14533 | 278700 |                                                             | GLY16SER  |
| xeroderma<br>pigmentosum<br>complementation<br>group A | D14533 | 278700 |                                                             | GLY58ARG  |
| xeroderma<br>pigmentosum<br>complementation<br>group A | D14533 | 278700 |                                                             | LEU78VAL  |
| xeroderma<br>pigmentosum<br>complementation            | D14533 | 278700 | EX6DEL                                                      |           |

|                                                        |               |        |                                                                     |           |
|--------------------------------------------------------|---------------|--------|---------------------------------------------------------------------|-----------|
| group A<br>xeroderma<br>pigmentosum<br>complementation | D14533        | 278700 | T insertion<br>nucleotide at either<br>nucleotide 14823 or<br>14824 | ASP52GLY  |
| group A<br>xeroderma<br>pigmentosum<br>complementation | D14533        | 278700 |                                                                     |           |
| group A<br>xeroderma<br>pigmentosum<br>complementation | D14533        | 278700 |                                                                     | GLY140ASP |
| group A<br>xeroderma<br>pigmentosum<br>complementation | D14533        | 278700 |                                                                     | ASP194GLU |
| group A<br>xeroderma<br>pigmentosum<br>complementation | D14533        | 278700 |                                                                     | TYR153TER |
| group A<br>metallothionein 1b                          | AH00151<br>0  | 156349 | none found                                                          |           |
| metallothionein 1e                                     | M10942        | 156351 | none found                                                          |           |
| metallothionein 1f                                     | M10943        | 156352 | none found                                                          |           |
| metallothionein 1g                                     | J03910        | 156353 | none found                                                          |           |
| metallothionein 2a                                     | NM_0059<br>53 | 156360 | BamHI                                                               |           |
| metallothionein 3                                      | NM_0059<br>54 | 139255 | none found                                                          |           |
| asparagine synthetase                                  | M27396        | 108370 | none found                                                          |           |

|                                         |        |        |                                 |  |
|-----------------------------------------|--------|--------|---------------------------------|--|
| ornithine<br>decarboxylase 1<br>(ODC1)  | M16650 | 165640 | none found                      |  |
| O6 alkylguanine-DNA<br>alkyltransferase | M60761 | 156569 | 1034A>G                         |  |
| O6 alkylguanine-DNA<br>alkyltransferase | M60761 | 156569 | 1099C>T                         |  |
| O6 alkylguanine-DNA<br>alkyltransferase | M60761 | 156569 | 79G>T                           |  |
| O6 alkylguanine-DNA<br>alkyltransferase | M60761 | 156569 | GGA to AGA gly160arg            |  |
| mismatch repair<br>protein hMSH2        | U03911 | 120435 | PRO622LEU                       |  |
| mismatch repair<br>protein hMSH2        | U03911 | 120435 | splice variant DEL 50<br>CODONS |  |
| mismatch repair<br>protein hMSH2        | U03911 | 120435 | ARG406TER                       |  |
| mismatch repair<br>protein hMSH2        | U03911 | 120435 | HIS639TYR                       |  |
| mismatch repair<br>protein hMSH2        | U03911 | 120435 | 3-BP DEL ASN596DEL              |  |
| mismatch repair<br>protein hMSH2        | U03911 | 120435 | C1801T GLN601TER                |  |
| mismatch repair<br>protein hMSH2        | U03911 | 120435 | ARG524PRO                       |  |
| mismatch repair<br>protein hMSH2        | U03911 | 120435 | 1-BP DEL<br>TGT705TT            |  |
| mismatch repair<br>protein hMSH2        | U03911 | 120435 | 22-BP INS 289 codon 97          |  |
| mismatch repair<br>protein hMSH2        | U03911 | 120435 | GLY322ASP                       |  |

|                                      |        |        |                                                          |
|--------------------------------------|--------|--------|----------------------------------------------------------|
| mismatch repair<br>protein hMSH2     | U03911 | 120435 | A-943+3-T DEL Exon 5                                     |
| mismatch repair<br>protein hMSH2     | U03911 | 120435 | C>T at codon 389                                         |
| mismatch repair<br>protein hMSH2     | U03911 | 120435 | 711bp CGA>TGA arg>ter                                    |
| mismatch repair<br>protein hMSH2     | U03911 | 120435 | C/T promoter                                             |
| mismatch repair<br>protein hMSH2     | U03911 | 120435 | CTT to TTT at phe>leu<br>codon 390                       |
| mismatch repair<br>protein hMSH2     | U03911 | 120435 | 1-bp insertion in<br>exon 12                             |
| mismatch repair<br>protein hMSH2     | U03911 | 120435 | codon 888 del C                                          |
| mismatch repair<br>protein hMSH2     | U03911 | 120435 | T-to-C exon 13                                           |
| cytochrome P450<br>aromatase (CYP19) | X13589 | 107910 | ARG435CYS                                                |
| cytochrome P450<br>aromatase (CYP19) | X13589 | 107910 | CYS437TYR                                                |
| cytochrome P450<br>aromatase (CYP19) | X13589 | 107910 | splice donor 29 extra amino<br>(GT>GC) of intron 6 acids |
| cytochrome P450<br>aromatase (CYP19) | X13589 | 107910 | ARG375CYS                                                |
| cytochrome P450<br>aromatase (CYP19) | X13589 | 107910 | 1-BP DEL, 408C frameshift                                |
| cytochrome P450<br>aromatase (CYP19) | X13589 | 107910 | GT to AT exon and<br>intron 3                            |
| cytochrome P450<br>aromatase (CYP19) | X13589 | 107910 | G-1094 -A ARG365GLN                                      |
| cytochrome P450<br>aromatase (CYP19) | X13589 | 107910 | G-->A at Val80 silent                                    |

|                         |        |        |                                                                                  |
|-------------------------|--------|--------|----------------------------------------------------------------------------------|
| aromatase (CYP19)       | X13589 | 107910 | G-to-A Val370-to-Met                                                             |
| cytochrome P450         |        |        |                                                                                  |
| aromatase (CYP19)       | X13589 | 107910 | (TTTA) <sub>n</sub> in intron 5                                                  |
| cytochrome P450         |        |        |                                                                                  |
| aromatase (CYP19)       | X13589 | 107910 | Arg264cys                                                                        |
| cytochrome P450         |        |        |                                                                                  |
| aromatase (CYP19)       | M11050 | 138040 | ASP641VAL                                                                        |
| glucocorticoid receptor |        |        |                                                                                  |
| glucocorticoid receptor | M11050 | 138040 | 4-BP DEL 2 bases of the<br>exon and the<br>first 2<br>nucleotides of<br>intron 6 |
| glucocorticoid receptor | M11050 | 138040 | LEU753PHE                                                                        |
| glucocorticoid receptor | M11050 | 138040 | ILE747THR                                                                        |
| glucocorticoid receptor | M11050 | 138040 | CYS736SER                                                                        |
| glucocorticoid receptor | M11050 | 138040 | CYS736THR                                                                        |
| glucocorticoid receptor | M11050 | 138040 | ASN363SER                                                                        |
| glucocorticoid receptor | M11050 | 138040 | Base-pair deletion in 32 amino acid<br>exon 9 deletion                           |
| glucocorticoid receptor | M11050 | 138040 | Q710X                                                                            |
| glucocorticoid receptor | M11050 | 138040 | L753F                                                                            |
| glucocorticoid receptor | M11050 | 138040 | trinucleotide Arg453<br>insertion                                                |
| glucocorticoid receptor | M11050 | 138040 | T insertion 1188 and frameshift<br>1189                                          |
| glucocorticoid receptor | M11050 | 138040 | A to G 3'-splice frameshift<br>junction of intron G                              |
| glucocorticoid receptor | M11050 | 138040 | BcII                                                                             |
| glucocorticoid receptor | M11050 | 138040 | TthIII1                                                                          |
| glucocorticoid receptor | U25029 | 138040 | none found                                                                       |

|                                                                          |                  |                  |                    |           |
|--------------------------------------------------------------------------|------------------|------------------|--------------------|-----------|
| alpha<br>glucocorticoid receptor                                         | X03348           | 138040           | none found         |           |
| beta<br>multidrug resistance<br>protein MDR1                             | X96395           | 171050           |                    | GLY185VAL |
| multidrug resistance<br>protein MDR1                                     | X96395           | 171050           |                    | Ser893Ala |
| multidrug resistance<br>protein MDR1                                     | X96395           | 171050           | HindIII            |           |
| progesterone receptor<br>insulin-like growth<br>factor binding protein 2 | M15716<br>X16302 | 264080<br>146731 | EcoRI              |           |
| insulin-like growth<br>factor binding protein 4                          | M62403           | 146733           | none found         |           |
| multidrug resistance<br>protein MDR2                                     | NM_0003<br>92    | 601107           | none found         |           |
| lipocortin 1/annexin 1                                                   | V00546           | 151690           | none found         |           |
| androgen receptor                                                        | M20132           | 313700           | PARTIAL DEL        | ARG773CYS |
| androgen receptor                                                        | M20132           | 313700           |                    | TRP717TER |
| androgen receptor                                                        | M20132           | 313700           |                    | VAL866MET |
| androgen receptor                                                        | M20132           | 313700           |                    | TRP794TER |
| androgen receptor                                                        | M20132           | 313700           |                    | LYS588TER |
| androgen receptor                                                        | M20132           | 313700           |                    | TYR761CYS |
| androgen receptor                                                        | M20132           | 313700           |                    | LYS882TER |
| androgen receptor                                                        | M20132           | 313700           |                    | ARG772CYS |
| androgen receptor                                                        | M20132           | 313700           |                    | ALA771THR |
| androgen receptor                                                        | M20132           | 313700           |                    | MET786VAL |
| androgen receptor                                                        | M20132           | 313700           |                    | VAL730MET |
| androgen receptor                                                        | M20132           | 313700           | (CAG) <sup>n</sup> |           |
| androgen receptor                                                        | M20132           | 313700           | ARG773HIS          |           |

|                   |        |        |                             |
|-------------------|--------|--------|-----------------------------|
| androgen receptor | M20132 | 313700 | ARG607GLN                   |
| androgen receptor | M20132 | 313700 | VAL865MET                   |
| androgen receptor | M20132 | 313700 | VAL865LEU                   |
| androgen receptor | M20132 | 313700 | ARG855HIS                   |
| androgen receptor | M20132 | 313700 | ILE869MET                   |
| androgen receptor | M20132 | 313700 | GLN60TER                    |
| androgen receptor | M20132 | 313700 | 5-KB DEL,EX E               |
| androgen receptor | M20132 | 313700 | 5-KB DEL, EX F,G            |
| androgen receptor | M20132 | 313700 | ARG608LYS                   |
| androgen receptor | M20132 | 313700 | ARG839HIS                   |
| androgen receptor | M20132 | 313700 | ARG839CYS                   |
| androgen receptor | M20132 | 313700 | THR877ALA                   |
| androgen receptor | M20132 | 313700 | LEU676PRO                   |
| androgen receptor | M20132 | 313700 | THR877SER                   |
| androgen receptor | M20132 | 313700 | HIS874TYR                   |
| androgen receptor | M20132 | 313700 | GLN902ARG                   |
| androgen receptor | M20132 | 313700 | ALA721THR                   |
| androgen receptor | M20132 | 313700 | SER647ASN                   |
| androgen receptor | M20132 | 313700 | LEU707ARG                   |
| androgen receptor | M20132 | 313700 | CYS579PHE                   |
| androgen receptor | M20132 | 313700 | PHE582TYR                   |
| androgen receptor | M20132 | 313700 | PRO546SER                   |
| androgen receptor | M20132 | 313700 | GLU2LYS                     |
| androgen receptor | M20132 | 313700 | MET780ILE                   |
| androgen receptor | M20132 | 313700 | ARG846HIS                   |
| androgen receptor | M20132 | 313700 | Insert of 69<br>nucleotides |
| androgen receptor | M20132 | 313700 | LEU172TER                   |
| androgen receptor | M20132 | 313700 | (CAA) <sub>n</sub>          |
| androgen receptor | M20132 | 313700 | (GGN) <sub>n</sub>          |
| androgen receptor | M20132 | 313700 | pro892ser                   |

|                     |        |        |                                 |
|---------------------|--------|--------|---------------------------------|
| androgen receptor   | M20132 | 313700 | 598 or 599 ter                  |
| androgen receptor   | M20132 | 313700 | Del T at 3286 frameshift        |
| androgen receptor   | M20132 | 313700 | Gln798Glu                       |
| androgen receptor   | M20132 | 313700 | G214R                           |
| androgen receptor   | M20132 | 313700 | G Codon 210 A                   |
| androgen receptor   | M20132 | 313700 | G Codon 211 A                   |
| androgen receptor   | M20132 | 313700 | Arg615His                       |
| androgen receptor   | M20132 | 313700 | Arg752Gln                       |
| androgen receptor   | M20132 | 313700 | C>T within exon B silent        |
| androgen receptor   | M20132 | 313700 | G2677A glu629arg                |
| androgen receptor   | M20132 | 313700 | Stu I                           |
| androgen receptor   | M20132 | 313700 | arg726leu                       |
| androgen receptor   | M20132 | 313700 | del1893 frameshift              |
| androgen receptor   | M20132 | 313700 | arg840his                       |
| androgen receptor   | M20132 | 313700 | Hind III                        |
| androgen receptor   | M20132 | 313700 | val 581 phe                     |
| androgen receptor   | M20132 | 313700 | MaeIII                          |
| androgen receptor   | M20132 | 313700 | CAG340TAG Gln>Ter               |
| androgen receptor   | M20132 | 313700 | gly743val                       |
| androgen receptor   | M20132 | 313700 | HpaII                           |
| androgen receptor   | M20132 | 313700 | HhaI                            |
| androgen receptor   | M20132 | 313700 | G2314A ala>thr                  |
| clustrin/TRPM-2     | M64722 | 185430 | asp317 his                      |
| clustrin/TRPM-2     | M64722 | 185430 | codon 328 (G-->A) asp328asp     |
| fos proto-oncogene  | K00650 | 164810 | T-->C transition in<br>intron 2 |
| myc proto-oncogene  | V00568 | 190080 | PRO59ALA                        |
| myc proto-oncogene  | V00568 | 190080 | PRO57SER                        |
| myc proto-oncogene  | V00568 | 190080 | ASN86THR                        |
| myc proto-oncogene  | V00568 | 190080 | GLU39ASP                        |
| bleomycin hydrolase | X92106 | 602403 | 1450A-G ILE443VAL               |



|                                               |           |        |                          |  |
|-----------------------------------------------|-----------|--------|--------------------------|--|
| estrogen receptor 1 (ESR1)                    | M12674    | 133430 | done                     |  |
| estrogen receptor 2 (ESR2)                    | X99101    | 601663 | done                     |  |
| trefoil factor 1/sP2                          | X00474    | 113710 |                          |  |
| Bcl-2 associated protein/bax                  | L22473    | 600040 | 1-BP INS Codons 38 to 41 |  |
| Bcl-2 associated protein/bax                  | L22473    | 600040 | 1-BP DEL Codons 38 to 41 |  |
| Bcl-2 associated protein/bax                  | L22473    | 600040 | GLY67ARG                 |  |
| Bcl-2 associated protein/bax                  | L22473    | 600040 | 7-BP DEL codons 38 to 41 |  |
| protein kinase C alpha                        | X52479    | 176960 | ASP294GLY                |  |
| protein kinase C beta 1                       | X06318    | 176970 | none found               |  |
| protein kinase C delta                        | L07861    | 176977 | none found               |  |
| protein kinase C mu                           | X75756    | *****  | none found               |  |
| protein kinase C theta                        | L01087    | 600448 | none found               |  |
| protein kinase C zeta                         | L14283    | 176982 | none found               |  |
| insulin-like growth factor binding protein 1  | NM_000596 | 146730 | none found               |  |
| insulin-like growth factor binding protein 10 | U62015    | 602369 | none found               |  |
| insulin-like growth factor binding protein 3  | NM_000598 | 146732 | none found               |  |
| insulin-like growth factor binding protein 5  | L27560    | 146734 | none found               |  |
| insulin-like growth factor binding protein 6  | M69054    | 146735 | none found               |  |
| insulin-like growth factor binding protein 6  | L19182    | 602867 | none found               |  |

|                          |         |        |                                |  |
|--------------------------|---------|--------|--------------------------------|--|
| factor binding protein 7 |         |        |                                |  |
| interferon gamma         | NM_0008 | 602376 | none found                     |  |
| receptor 2 (IFNGR2)      | 74      |        |                                |  |
| interferon alpha         | X77722  | 107450 | none found                     |  |
| receptor 1 (IFNAR1)      |         |        |                                |  |
| interferon alpha         | U68755  | 147569 | Gln64Arg                       |  |
| receptor 2 (IFNAR2)      |         |        |                                |  |
| interferon beta1         | V00546  | 147640 | none found                     |  |
| (IFNb1)                  |         |        |                                |  |
| interferon gamma         | L07633  | 147570 | CA repeat itron 1              |  |
| (IFNg)                   |         |        |                                |  |
| interferon gamma         | L07633  | 147570 | CGA to CAA Arg140Gln           |  |
| (IFNg)                   |         |        |                                |  |
| interferon gamma         | L07633  | 147570 | G5644A                         |  |
| (IFNg)                   |         |        |                                |  |
| interferon gamma         | J03143  | 107470 | 395C-A SER-TER                 |  |
| receptor 1 (IFNGR1)      |         |        |                                |  |
| interferon gamma         | J03143  | 107470 | 1-BP DEL frameshift            |  |
| receptor 1 (IFNGR1)      |         |        |                                |  |
| interferon gamma         | J03143  | 107470 | ILE87THR                       |  |
| receptor 1 (IFNGR1)      |         |        |                                |  |
| interferon gamma         | J03143  | 107470 | 4-BP INS 104 to 107 frameshift |  |
| receptor 1 (IFNGR1)      |         |        |                                |  |
| interferon gamma         | J03143  | 107470 | IVS3                           |  |
| receptor 1 (IFNGR1)      |         |        |                                |  |
| interferon gamma         | J03143  | 107470 | 4-BP DEL truncated             |  |
| receptor 1 (IFNGR1)      |         |        | protein                        |  |
| interferon gamma         | J03143  | 107470 | Val14Met                       |  |
| receptor 1 (IFNGR1)      |         |        |                                |  |
| interferon gamma         | J03143  | 107470 | TaqI                           |  |
| receptor 1 (IFNGR1)      |         |        |                                |  |

|                                            |        |        |                                 |
|--------------------------------------------|--------|--------|---------------------------------|
| interferon omegal<br>(IFNw1)               | X02669 | 147553 | none found                      |
| interleukin 1 alpha<br>(IL1a)              | M15329 | 147760 | C to T -889                     |
| interleukin 1 alpha<br>(IL1a)              | M15329 | 147760 | Dinucleotide repeat             |
| interleukin 1 alpha<br>(IL1a)              | M15329 | 147760 | 46 bp tandem repeat<br>intron 6 |
| interleukin 1 beta<br>(IL1b)               | K02770 | 147720 | TaqI                            |
| interleukin 1 beta<br>(IL1b)               | K02770 | 147720 | +5887 C --> T                   |
| interleukin 1 beta<br>(IL1b)               | K02770 | 147720 | position -511                   |
| interleukin 1 beta<br>(IL1b)               | K02770 | 147720 | exon 5 (position<br>+3953)      |
| interleukin 1 beta<br>(IL1b)               | K02770 | 147720 | Asp106Asn                       |
| interleukin 1 receptor<br>(IL-1R)          | M27492 | 147810 | PstI                            |
| interleukin 10 (IL10)                      | M57627 | 124092 | G -1082 A                       |
| interleukin 10 (IL10)                      | M57627 | 124092 | C-to-A 571                      |
| interleukin 10 (IL10)                      | M57627 | 124092 | A-597 C                         |
| interleukin 10 (IL10)                      | M57627 | 124092 | T -824 C                        |
| interleukin 10 (IL10)                      | M57627 | 124092 | second dinucleotide<br>repeat   |
| interleukin 10 (IL10)                      | M57627 | 124092 | A -592 C                        |
| interleukin 10 (IL10)                      | M57627 | 124092 | 2 CA repeat                     |
| interleukin 10 receptor<br>alpha (IL-10Ra) | U00672 | 146933 | none found                      |
| interleukin 11 (IL11)                      | X58377 | 147681 | 5' dinucleotide                 |

|                                            |               |        |                              |
|--------------------------------------------|---------------|--------|------------------------------|
| interleukin 12a (IL12a)                    | M65271        | 161560 | repeat<br>none found         |
| interleukin 12b (IL12b)                    | M65272        | 161561 | 4.4-KB DEL                   |
| interleukin 13 (IL13)                      | X69079        | 147683 | none found                   |
| interleukin 15 (IL15)                      | U14407        | 600554 | none found                   |
| interleukin 15 receptor<br>alpha (IL-15Ra) | U31628        | 601070 | none found                   |
| interleukin 16 (IL16)                      | NM_0045<br>13 | 603035 | none found                   |
| interleukin 18 (IL18)                      | *****         | 600953 | none found                   |
| interleukin 2 (IL2)                        | X01586        | 147680 | -330                         |
| interleukin 2 (IL2)                        | X01586        | 147680 | 166                          |
| interleukin 2 (IL2)                        | X01586        | 147680 | Dinucleotide Repeat          |
| interleukin 2 (IL2)                        | X01586        | 147680 | AUUUA motif<br>deleted       |
| interleukin 2 receptor<br>alpha (IL-2Ra)   | X01057        | 147730 | 4-BP DEL 60 to 64 frameshift |
| interleukin 2 receptor<br>alpha (IL-2Ra)   | X01057        | 147730 | TaqI                         |
| interleukin 2 receptor<br>beta (IL-2Rb)    | M26062        | 146710 | CA repeat                    |
| interleukin 2 receptor<br>gamma (IL-2Rg)   | D11086        | 308380 | LYS97TER                     |
| interleukin 2 receptor<br>gamma (IL-2Rg)   | D11086        | 308380 | ARG267TER                    |
| interleukin 2 receptor<br>gamma (IL-2Rg)   | D11086        | 308380 | SER286TER                    |
| interleukin 2 receptor<br>gamma (IL-2Rg)   | D11086        | 308380 | CYS62TER                     |
| interleukin 2 receptor<br>gamma (IL-2Rg)   | D11086        | 308380 | GLY114ASP                    |

|                                          |        |        |                                      |                    |
|------------------------------------------|--------|--------|--------------------------------------|--------------------|
| interleukin 2 receptor<br>gamma (IL-2Rg) | D11086 | 308380 | G-to-A first position<br>of intron 3 | ILE153ASN          |
| interleukin 2 receptor<br>gamma (IL-2Rg) | D11086 | 308380 |                                      |                    |
| interleukin 2 receptor<br>gamma (IL-2Rg) | D11086 | 308380 |                                      | LEU271GLN          |
| interleukin 2 receptor<br>gamma (IL-2Rg) | D11086 | 308380 | 9-BP DUP                             | GLN-HIS-TRP<br>INS |
| interleukin 2 receptor<br>gamma (IL-2Rg) | D11086 | 308380 |                                      | CYS115ARG          |
| interleukin 2 receptor<br>gamma (IL-2Rg) | D11086 | 308380 |                                      | ARG285GLN          |
| interleukin 2 receptor<br>gamma (IL-2Rg) | D11086 | 308380 |                                      | ARG222CYS          |
| interleukin 2 receptor<br>gamma (IL-2Rg) | D11086 | 308380 | 690-691 hotspot                      |                    |
| interleukin 3 (IL3)                      | M20137 | 147740 | none found                           |                    |
| interleukin 3 alpha<br>receptor (IL-3aR) | M74782 | 308385 | none found                           |                    |
| interleukin 4 (IL4)                      | M13982 | 147780 | C-589T                               |                    |
| interleukin 4 (IL4)                      | M13982 | 147780 | Dinucleotide Repeat<br>intron 2      |                    |
| interleukin 4 (IL4)                      | M13982 | 147780 | -285 C-T                             |                    |
| interleukin 4 receptor<br>(IL-4R)        | X52425 | 147781 | -81 A-G                              | GLN576ARG          |
| interleukin 4 receptor<br>(IL-4R)        | X52425 | 147781 |                                      | ILE50VAL           |
| interleukin 4 receptor<br>(IL-4R)        | X52425 | 147781 |                                      | S503P              |
| interleukin 5 (IL5)                      | X04688 | 147850 | none found                           |                    |

|                                            |        |        |                                      |           |
|--------------------------------------------|--------|--------|--------------------------------------|-----------|
| interleukin 5 receptor<br>alpha (IL-5Ra)   | M96652 | 147851 | Dinucleotide repeat                  |           |
| interleukin 6 receptor<br>(IL-6R) (20)     | M20566 | 147880 | dinucleotide (CA)                    |           |
| interleukin 7 (IL7)                        | J04156 | 146660 | none found                           | THR66ILE  |
| interleukin 7 receptor<br>(IL-7R)          | M29696 | 146661 |                                      | ILE138VAL |
| interleukin 7 receptor<br>(IL-7R)          | M29696 | 146661 | AG-to-AA splice<br>junction intron 4 |           |
| interleukin 7 receptor<br>(IL-7R)          | M29696 | 146661 | trp217 to ter                        |           |
| interleukin 8 (IL8)                        | M26383 | 146930 | HindIII                              |           |
| interleukin 8 receptor<br>alpha (IL-8Ra)   | M68932 | 146929 | none found                           |           |
| interleukin 8 receptor<br>beta (IL-8Rb)    | M94582 | 146928 | none found                           |           |
| interleukin 9 (IL9)                        | X17543 | 146931 | Dinucleotide repeat                  |           |
| interleukin 9 receptor<br>(IL-9R)          | M84747 | 300007 | none found                           |           |
| interleukin receptor 11<br>alpha (IL-11a)  | U32324 | 600939 | none found                           |           |
| interleukin receptor 12<br>beta (IL-12b)   | U03187 | 601604 |                                      | GLN32TER  |
| interleukin receptor 12<br>beta (IL-12b)   | U03187 | 601604 |                                      | GLN376TER |
| interleukin receptor 12<br>beta (IL-12b)   | U03187 | 601604 | 409-549DEL frameshift                |           |
| interleukin receptor 12<br>beta2 (IL-12b2) | U03187 | 601642 | none found                           |           |

|                                              |               |        |                       |
|----------------------------------------------|---------------|--------|-----------------------|
| interleukin receptor 13<br>alpha (IL-13a)    | S80963        | 300119 | none found            |
| interleukin receptor 13<br>alpha2 (IL-13a2)  | X95302        | 300130 | none found            |
| lipocortin 2/annexin 2                       | D00017        | 151740 | none found            |
| lipocortin 3/annexin 3                       | M20560        | 106490 | tandem repeat<br>TAAA |
| lipocortin 3/annexin 3                       | M20560        | 106490 | SalI                  |
| lipocortin 3/annexin 3                       | M20560        | 106490 | BglII                 |
| lipocortin 5/annexin 5                       | NM_0011<br>54 | 131230 | EcoRI                 |
| lipocortin 5/annexin 5                       | NM_0011<br>54 | 131230 | PvuII                 |
| lipocortin 7/annexin 7<br>(splice variant 1) | NM_0040<br>34 | 186360 | none found            |
| lipocortin 7/annexin 7<br>(splice variant 2) | NM_0011<br>56 | 186360 | none found            |
| trefoil factor 2/TFF2                        | X51698        | 182590 | 25 bp tandem repeat   |
| trefoil factor 3/sP2                         | L08044        | 600633 | none found            |

Table 19. Identified  
Variances in Genes or  
Related Pathways  
involved in  
Neurological or  
Psychiatric Disease

|                                           |        |        |           |
|-------------------------------------------|--------|--------|-----------|
| Nicotinic, Cholinergic<br>receptor beta 1 | X14830 | 100710 | LEU263MET |
| Nicotinic, Cholinergic<br>receptor beta 1 | X14830 | 100710 | VAL266MET |

|                                                           |               |        |                     |  |
|-----------------------------------------------------------|---------------|--------|---------------------|--|
| Nicotinic, Cholinergic<br>receptor, muscle d              | X55019        | 100720 | none found          |  |
| Nicotinic, Cholinergic<br>receptor epsilon<br>polypeptide | X66403        | 100725 | ARG147LEU           |  |
| Nicotinic, Cholinergic<br>receptor epsilon<br>polypeptide | X66403        | 100725 | ARG64TER            |  |
| Nicotinic, Cholinergic<br>receptor epsilon<br>polypeptide | X66403        | 100725 | LEU269PHE           |  |
| Nicotinic, Cholinergic<br>receptor epsilon<br>polypeptide | X66403        | 100725 | PRO121LEU           |  |
| Nicotinic, Cholinergic<br>receptor epsilon<br>polypeptide | X66403        | 100725 | THR264PRO           |  |
| Nicotinic, Cholinergic<br>receptor, muscle g              | NM_0051<br>99 | 100730 | none found          |  |
| Acetylcholinesterase/A<br>CHE                             | M55040        | 100740 | 1431 C/T 446 silent |  |
| Acetylcholinesterase/A<br>CHE                             | M55040        | 100740 | 408 G/C arg561pro   |  |
| Acetylcholinesterase/A<br>CHE                             | M55040        | 100740 | HIS322ASN           |  |
| adenosine deaminase                                       | NM_0000<br>22 | 102700 | LYS80ARG            |  |
| adenosine deaminase                                       | NM_0000<br>22 | 102700 | ARG101TRP           |  |
| adenosine deaminase                                       | NM_0000<br>22 | 102700 | ARG101GLN           |  |



|                               |        |                        |
|-------------------------------|--------|------------------------|
| adenosine deaminase NM_000022 | 102700 | ARG211HIS              |
| adenosine deaminase NM_000022 | 102700 | LEU304ARG              |
| adenosine deaminase NM_000022 | 102700 | ALA329VAL              |
| adenosine deaminase NM_000022 | 102700 | ALA39VAL               |
| adenosine deaminase NM_000022 | 102700 | 3.25-KB DEL            |
| adenosine deaminase NM_000022 | 102700 | PRO297GLN              |
| adenosine deaminase NM_000022 | 102700 | ARG76TRP               |
| adenosine deaminase NM_000022 | 102700 | ARG149GLN              |
| adenosine deaminase NM_000022 | 102700 | PRO274LEU              |
| adenosine deaminase NM_000022 | 102700 | LEU107PRO              |
| adenosine deaminase NM_000022 | 102700 | ARG211CYS              |
| adenosine deaminase NM_000022 | 102700 | ALA215THR              |
| adenosine deaminase NM_000022 | 102700 | GLY216ARG              |
| adenosine deaminase NM_000022 | 102700 | IVS3AS, A-G, -2 EX4DEL |
| adenosine deaminase NM_000022 | 102700 | ARG156CYS              |
| adenosine deaminase NM_000022 | 102700 | SER291LEU              |

|                               |        |                                        |           |
|-------------------------------|--------|----------------------------------------|-----------|
| adenosine deaminase NM_000022 | 102700 | IVS10AS, G-A, -34                      |           |
| adenosine deaminase NM_000022 | 102700 |                                        | ASP8ASN   |
| adenosine deaminase NM_000022 | 102700 | IVS2DS, G-A, +1                        |           |
| adenosine deaminase NM_000022 | 102700 | 7-BP INS, IVS8AS                       |           |
| adenosine deaminase NM_000022 | 102700 | IVS1DS, G-C, +1                        |           |
| adenosine deaminase NM_000022 | 102700 |                                        | GLY74VAL  |
| adenosine deaminase NM_000022 | 102700 | IVS5DS, G-A, +1, EX5 DEL<br>116-BP DEL |           |
| adenosine deaminase NM_000022 | 102700 |                                        | LEU152MET |
| adenosine deaminase NM_000022 | 102700 |                                        | THR233ILE |
| adenosine deaminase NM_000022 | 102700 |                                        | TYR97CYS  |
| adenosine deaminase NM_000022 | 102700 |                                        | LEU106VAL |
| adenosine deaminase NM_000022 | 102700 |                                        | G74C      |
| adenosine deaminase NM_000022 | 102700 |                                        | V129M     |
| adenosine deaminase NM_000022 | 102700 |                                        | G140E     |
| adenosine deaminase NM_000022 | 102700 |                                        | R149W     |

|                                                 |        |                                           |
|-------------------------------------------------|--------|-------------------------------------------|
| adenosine deaminase NM_000022                   | 102700 | Q199P                                     |
| adenosine deaminase NM_000022                   | 102700 | 462delG                                   |
| adenosine deaminase NM_000022                   | 102700 | E337del                                   |
| adenosine deaminase NM_000022                   | 102700 | tetranucleotide repeat                    |
| adenosine deaminase NM_000022                   | 102700 | Q3X                                       |
| adenosine deaminase NM_000022                   | 102700 | R142Q                                     |
| adenosine deaminase NM_000022                   | 102700 | R142X                                     |
| adenosine deaminase NM_000022                   | 102700 | PstI                                      |
| adenosine deaminase NM_000022                   | 102700 | G to A at the invariant 5' GT of intron 7 |
| adenosine deaminase NM_000022                   | 102700 | Glu 217 Lys                               |
| adenosine deaminase NM_000022                   | 102700 | del exon 7                                |
| adenosine deaminase NM_000022                   | 102700 | Apa I                                     |
| Adenosine A1 Receptor; Adora1/G protein-coupled | 102775 | 1777C/A                                   |
| Adenosine A1 Receptor; Adora1/G protein-coupled | 102775 | 1827C/T                                   |

|                                                       |        |        |              |
|-------------------------------------------------------|--------|--------|--------------|
| Adenosine A1<br>Receptor; Adora1/G<br>protein-coupled | L22214 | 102775 | 1904C/T      |
| Adenosine A1<br>Receptor; Adora1/G<br>protein-coupled | L22214 | 102775 | 2126G/T      |
| Adenosine A1<br>Receptor; Adora1/G<br>protein-coupled | L22214 | 102775 | 2294insT     |
| Adenosine A1<br>Receptor; Adora1/G<br>protein-coupled | L22214 | 102775 | 267 + 275C/T |
| Adenosine A1<br>Receptor; Adora1/G<br>protein-coupled | L22214 | 102775 | 2776C/T      |
| Adenosine A1<br>Receptor; Adora1/G<br>protein-coupled | L22214 | 102775 | 2777del36    |
| Adenosine A1<br>Receptor; Adora1/G<br>protein-coupled | L22214 | 102775 | 2819T/G      |
| Adenosine A1<br>Receptor; Adora1/G<br>protein-coupled | L22214 | 102775 | 805T/G       |
| Adenosine A1<br>Receptor; Adora1/G<br>protein-coupled | L22214 | 102775 | 48T/A        |
| Adenosine A1<br>Receptor; Adora1/G<br>protein-coupled | L22214 | 102775 | 716T/G       |
| Adenosine A2                                          | X68486 | 102776 | 1083C/T      |

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|                                                                                |        |        |               |             |
|--------------------------------------------------------------------------------|--------|--------|---------------|-------------|
| Receptor; Adora2a/G<br>protein-coupled<br>Adenosine A2                         | X68486 | 102776 | 405C/T        |             |
| Receptor; Adora2a/G<br>protein-coupled<br>Adenosine A2                         | X68486 | 102776 | 432C/T        |             |
| Receptor; Adora2a/G<br>protein-coupled<br>Adenosine A2                         | X68486 | 102776 |               | Gly-340-Ser |
| Receptor-<br>like/ADORA2L1<br>adenylate-cyclase<br>activating polypeptide<br>1 | *****  | 102777 | none found    |             |
| receptor/ADCYAP1R1<br>alpha-2a-adrenergic<br>receptor; ADRA2A                  | D17516 | 102981 | none found    |             |
| alpha-2a-adrenergic<br>receptor; ADRA2A                                        | M18415 | 104210 | -1291         |             |
| alpha-2a-adrenergic<br>receptor; ADRA2A                                        | M18415 | 104210 | DraI          |             |
| alpha-2a-adrenergic<br>receptor; ADRA2A                                        | M18415 | 104210 | HhaI          |             |
| alpha-2a-adrenergic<br>receptor; ADRA2A                                        | M18415 | 104210 | MspI promoter |             |
| alpha-1a-adrenergic<br>receptor; ADRA1A                                        | M76446 | 104219 | none found    |             |
| alpha-1b-adrenergic<br>receptor; ADRA1B                                        | L31773 | 104220 | none found    |             |
| alpha-1c-adrenergic                                                            | D25235 | 104221 | PstI          |             |

|                     |          |        |                     |  |
|---------------------|----------|--------|---------------------|--|
| receptor; ADRA1C    | M76446   | 104222 | none found          |  |
| alpha-1d-adrenergic |          |        |                     |  |
| receptor; ADRA1D    | J03853   | 104250 | (CA)n               |  |
| alpha-2c-adrenergic |          |        |                     |  |
| receptor; ADRA2C    | AF005900 | 104260 | none found          |  |
| alpha-2b-adrenergic |          |        |                     |  |
| receptor; ADRA2B    | NM_0000  | 104311 | IVS8AS, G-T, -1,    |  |
| presenilin 1        | 21       |        | EX9DEL              |  |
| presenilin 1        | NM_0000  | 104311 | 1-BP DEL, G         |  |
| presenilin 1        | 21       |        |                     |  |
| presenilin 1        | NM_0000  | 104311 | intron 3' to exon 8 |  |
| presenilin 1        | 21       |        |                     |  |
| presenilin 1        | NM_0000  | 104311 | T/G intron 9        |  |
| presenilin 1        | 21       |        |                     |  |
| presenilin 1        | NM_0000  | 104311 | HIS163ARG           |  |
| presenilin 1        | 21       |        |                     |  |
| presenilin 1        | NM_0000  | 104311 | ALA246GLU           |  |
| presenilin 1        | 21       |        |                     |  |
| presenilin 1        | NM_0000  | 104311 | ALA426PRO           |  |
| presenilin 1        | 21       |        |                     |  |
| presenilin 1        | NM_0000  | 104311 | ARG278THR           |  |
| presenilin 1        | 21       |        |                     |  |
| presenilin 1        | NM_0000  | 104311 | CYS410TYR           |  |
| presenilin 1        | 21       |        |                     |  |
| presenilin 1        | NM_0000  | 104311 | GLU120ASP           |  |
| presenilin 1        | 21       |        |                     |  |
| presenilin 1        | NM_0000  | 104311 | GLU280ALA           |  |
| presenilin 1        | 21       |        |                     |  |
| presenilin 1        | NM_0000  | 104311 | GLU280GLY           |  |
| presenilin 1        | 21       |        |                     |  |

|                       |           |        |           |
|-----------------------|-----------|--------|-----------|
| presenilin 1          | NM_000021 | 104311 | Glu318Gly |
| presenilin 1          | NM_000021 | 104311 | gly378glu |
| presenilin 1          | NM_000021 | 104311 | HIS163TYR |
| presenilin 1          | NM_000021 | 104311 | LEU250SER |
| presenilin 1          | NM_000021 | 104311 | Leu262Phe |
| presenilin 1          | NM_000021 | 104311 | Leu282Arg |
| presenilin 1          | NM_000021 | 104311 | LEU286VAL |
| presenilin 1          | NM_000021 | 104311 | lys123glu |
| presenilin 1          | NM_000021 | 104311 | MET139VAL |
| presenilin 1          | NM_000021 | 104311 | MET146ILE |
| presenilin 1          | NM_000021 | 104311 | MET146LEU |
| presenilin 1          | NM_000021 | 104311 | MET146VAL |
| presenilin 1          | NM_000021 | 104311 | PRO267SER |
| presenilin 1          | NM_000021 | 104311 | Pro436Gln |
| presenilin 1          | NM_000021 | 104311 | Ser169Leu |
| Human cerebrovascular | M16765    | 104760 |           |

[illegible]



| E/APOE                   | 41        | creates 2<br>abnormally<br>spliced mRNA<br>forms     |
|--------------------------|-----------|------------------------------------------------------|
| apolipoprotein<br>E/APOE | NM_000041 | C305G Proline84Arginine                              |
| apolipoprotein<br>E/APOE | NM_000041 | C460A Arginine136Serine                              |
| apolipoprotein<br>E/APOE | NM_000041 | C478T Arg142142Cys142                                |
| apolipoprotein<br>E/APOE | NM_000041 | C487T Arginine145Cysteine                            |
| apolipoprotein<br>E/APOE | NM_000041 | C526T Arginine158Cysteine                            |
| apolipoprotein<br>E/APOE | NM_000041 | C736T Arginine228Cysteine                            |
| apolipoprotein<br>E/APOE | NM_000041 | C805G Arg251251Gly251                                |
| apolipoprotein<br>E/APOE | NM_000041 | G144deletion Leucine60Termination Codon (frameshift) |
| apolipoprotein<br>E/APOE | NM_000041 | G349A Ala9999Thr99                                   |
| apolipoprotein<br>E/APOE | NM_000041 | G434A Gly127127Asp127                                |
| apolipoprotein<br>E/APOE | NM_000041 | G455A Arginine134Glutamine                           |
| apolipoprotein<br>E/APOE | NM_000041 | G488A Arginine145Histidine                           |
| apolipoprotein<br>E/APOE | NM_000041 | G568C Ala152Proline                                  |

|                                                |           |        |                                                                      |
|------------------------------------------------|-----------|--------|----------------------------------------------------------------------|
| apolipoprotein<br>E/APOE                       | NM_000041 | 107741 | G61A Glutamic<br>Acid3Lysine                                         |
| apolipoprotein<br>E/APOE                       | NM_000041 | 107741 | G683A Tryptophan210<br>Termination<br>Codon                          |
| apolipoprotein<br>E/APOE                       | NM_000041 | 107741 | G725A Arg224224Gln224                                                |
| apolipoprotein<br>E/APOE                       | NM_000041 | 107741 | G875A Arginine274His<br>tidine                                       |
| apolipoprotein<br>E/APOE                       | NM_000041 | 107741 | G91A Glutamic<br>Acid13Lysine                                        |
| apolipoprotein<br>E/APOE                       | NM_000041 | 107741 | GAG-GAG844- Glu244/Glu245<br>849AAG-AAG 244-<br>245Lys244/Lys<br>245 |
| apolipoprotein<br>E/APOE                       | NM_000041 | 107741 | T137C Leucine28Proline                                               |
| apolipoprotein<br>E/APOE                       | NM_000041 | 107741 | T388C Cysteine112Arg<br>inine                                        |
| apolipoprotein<br>E/APOE                       | NM_000041 | 107741 | T761A Valine236Glutamic<br>Acid                                      |
| Aromatic L-Amino<br>Acid                       | M76180    | 107930 | SspI                                                                 |
| Decarboxylase/AADC/<br>dopa decarboxylase      |           |        |                                                                      |
| Benzodiazepine<br>receptor, peripheral<br>type | NM_000714 | 109610 | none found                                                           |
| beta-1-adrenergic<br>receptor; Adrb1           | J03019    | 109630 | Bgl I.                                                               |
| beta-1-adrenergic                              | J03019    | 109630 | C1165G ARG389GLY                                                     |

|                                                                  |           |        |             |           |
|------------------------------------------------------------------|-----------|--------|-------------|-----------|
| receptor; Adrb1<br>beta-adrenergic<br>receptor kinase<br>1/BARK1 | NM_001619 | 109635 | none found  |           |
| Beta-Adrenergic<br>Receptor Kinase 2;<br>Adrbk2                  | X69117    | 109636 | none found  |           |
| Beta-2-Adrenergic<br>Receptor; Adrb2                             | M15169    | 109690 | Fnu4HI      |           |
| Beta-2-Adrenergic<br>Receptor; Adrb2                             | M15169    | 109690 | A-->G -1343 |           |
| Beta-2-Adrenergic<br>Receptor; Adrb2                             | M15169    | 109690 | C-->G -468  |           |
| Beta-2-Adrenergic<br>Receptor; Adrb2                             | M15169    | 109690 | G-->A -1023 |           |
| Beta-2-Adrenergic<br>Receptor; Adrb2                             | M15169    | 109690 | G-->A -654  |           |
| Beta-2-Adrenergic<br>Receptor; Adrb2                             | M15169    | 109690 | T-->A -1429 |           |
| Beta-2-Adrenergic<br>Receptor; Adrb2                             | M15169    | 109690 | T-->C -20   |           |
| Beta-2-Adrenergic<br>Receptor; Adrb2                             | M15169    | 109690 | T-->C -367  |           |
| Beta-2-Adrenergic<br>Receptor; Adrb2                             | M15169    | 109690 | T-->C -47   |           |
| Beta-2-Adrenergic<br>Receptor; Adrb2                             | M15169    | 109690 |             | ARG16GLY  |
| Beta-2-Adrenergic<br>Receptor; Adrb2                             | M15169    | 109690 |             | GLN27GLU  |
| Beta-2-Adrenergic<br>Receptor; Adrb2                             | M15169    | 109690 |             | Thr164Ile |

|                                                 |           |        |                 |
|-------------------------------------------------|-----------|--------|-----------------|
| Beta-2-Adrenergic Receptor; Adrb2               | M15169    | 109690 | val 34 met      |
| Beta-3-Adrenergic Receptor; Adrb3               | X70811    | 109691 | intron 1 g1856t |
| Beta-3-Adrenergic Receptor; Adrb3               | X70811    | 109691 | TRP64ARG        |
| serotonin 5-HT receptors 5-HT1A, G              | X57829    | 109760 | RsaI            |
| protein-coupled bradykinin receptor B2/BDKRB2 G | NM_000623 | 113503 | -143C/T         |
| protein-coupled bradykinin receptor B2/BDKRB2 G | NM_000623 | 113503 | -412C/G         |
| protein-coupled bradykinin receptor B2/BDKRB2 G | NM_000623 | 113503 | -536C/T         |
| protein-coupled bradykinin receptor B2/BDKRB2 G | NM_000623 | 113503 | -640T/C         |
| protein-coupled bradykinin receptor B2/BDKRB2 G | NM_000623 | 113503 | -649insG        |
| protein-coupled bradykinin receptor B2/BDKRB2 G | NM_000623 | 113503 | -704C/T         |
| protein-coupled bradykinin receptor B2/BDKRB2 G | NM_000623 | 113503 | -78C/T          |
| protein-coupled bradykinin receptor             | NM_0006   | 113503 | -845C/T         |

|                     |               |        |                                |      |  |
|---------------------|---------------|--------|--------------------------------|------|--|
| B2/BDKRB2 G         | 23            |        |                                |      |  |
| protein-coupled     |               |        |                                |      |  |
| bradykinin receptor |               |        |                                |      |  |
| B2/BDKRB2 G         | NM_0006<br>23 | 113503 | 9 bp de (-)21-29               |      |  |
| protein-coupled     |               |        |                                |      |  |
| bradykinin receptor |               |        |                                |      |  |
| B2/BDKRB2 G         | NM_0006<br>23 | 113503 | C>T promoter 54                |      |  |
| protein-coupled     |               |        |                                |      |  |
| bradykinin receptor |               |        |                                |      |  |
| B2/BDKRB2 G         | NM_0006<br>23 | 113503 | repeat 3'UTR                   |      |  |
| protein-coupled     |               |        |                                |      |  |
| bradykinin receptor |               |        |                                |      |  |
| B2/BDKRB2 G         | NM_0006<br>23 | 113503 | tandem repeat near<br>promoter |      |  |
| protein-coupled     |               |        |                                |      |  |
| bradykinin receptor |               |        |                                |      |  |
| B2/BDKRB2 G         | NM_0006<br>23 | 113503 |                                | R14C |  |
| protein-coupled     |               |        |                                |      |  |
| bradykinin receptor |               |        |                                |      |  |
| B2/BDKRB2 G         | NM_0006<br>23 | 113503 |                                | T21M |  |
| protein-coupled     |               |        |                                |      |  |
| bradykinin receptor |               |        |                                |      |  |
| B2/BDKRB2 G         | NM_0006<br>23 | 113503 |                                |      |  |
| protein-coupled     |               |        |                                |      |  |
| L-type voltage      |               |        |                                |      |  |
| dependent calcium   |               |        |                                |      |  |
| channel alpha 1C    |               |        |                                |      |  |
| subunit/CACNA1C     |               |        |                                |      |  |
| L-type voltage      |               |        |                                |      |  |
| dependent calcium   |               |        |                                |      |  |
| channel alpha 1S    |               |        |                                |      |  |
| subunit/CACNA1S     |               |        |                                |      |  |
| L-type voltage      |               |        |                                |      |  |
| dependent calcium   |               |        |                                |      |  |
| channel alpha 1S    |               |        |                                |      |  |

|                      |         |        |  |                    |
|----------------------|---------|--------|--|--------------------|
| subunit/CACNA1S      |         |        |  |                    |
| L-type voltage       | NM_0000 | 114208 |  | ARG1239HIS         |
| dependent calcium    | 69      |        |  |                    |
| channel alpha 1S     |         |        |  |                    |
| subunit/CACNA1S      |         |        |  |                    |
| L-type voltage       | NM_0000 | 114208 |  | ARG528HIS          |
| dependent calcium    | 69      |        |  |                    |
| channel alpha 1S     |         |        |  |                    |
| subunit/CACNA1S      |         |        |  |                    |
| calpain, large       | NM_0000 | 114240 |  | ARG572GLN          |
| polypeptide          | 70      |        |  |                    |
| L3/CAPN3             |         |        |  |                    |
| calpain, large       | NM_0000 | 114240 |  | ARG110TER          |
| polypeptide          | 70      |        |  |                    |
| L3/CAPN3             |         |        |  |                    |
| calpain, large       | NM_0000 | 114240 |  | ARG769GLN          |
| polypeptide          | 70      |        |  |                    |
| L3/CAPN3             |         |        |  |                    |
| calpain, large       | NM_0000 | 114240 |  | PRO319LEU          |
| polypeptide          | 70      |        |  |                    |
| L3/CAPN3             |         |        |  |                    |
| calpain, large       | NM_0000 | 114240 |  | SER86PHE           |
| polypeptide          | 70      |        |  |                    |
| L3/CAPN3             |         |        |  |                    |
| cannabinoid receptor | NM_0018 | 114610 |  | 1359G-->A silent   |
| 1/G protein-         | 40      |        |  |                    |
| coupled/CNR1         |         |        |  |                    |
| Catechol-O-          | M58525  | 116790 |  | 186C > T at exon 3 |
| Methyltransferase    |         |        |  |                    |
| Catechol-O-          | M58525  | 116790 |  | 408C > G at exon 4 |
| Methyltransferase    |         |        |  |                    |

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|                                                                              |        |        |                              |  |
|------------------------------------------------------------------------------|--------|--------|------------------------------|--|
| Catechol-O-Methyltransferase                                                 | M58525 | 116790 | 472G > A at exon 4           |  |
| Catechol-O-Methyltransferase                                                 | M58525 | 116790 | 597G > A at exon 5           |  |
| Catechol-O-Methyltransferase                                                 | M58525 | 116790 | 821-827insC at the 3'        |  |
| Catechol-O-Methyltransferase                                                 | M58525 | 116790 | BglI                         |  |
| Catechol-O-Methyltransferase                                                 | M58525 | 116790 | C256G silent                 |  |
| Catechol-O-Methyltransferase                                                 | M58525 | 116790 | G/A1947                      |  |
| Catechol-O-Methyltransferase                                                 | M58525 | 116790 | MspI                         |  |
| Catechol-O-Methyltransferase                                                 | M58525 | 116790 | NlaIII                       |  |
| Catechol-O-Methyltransferase                                                 | M58525 | 116790 | val-108-met                  |  |
| Catechol-O-Methyltransferase                                                 | M58525 | 116790 | Val158-->Met                 |  |
| Methyltransferase cathepsin B/b-aCTSBmyloid precursor protein secretase/CTSB | M14221 | 116810 | 10-bp insertion in the 3'-UT |  |
| cathepsin B/b-aCTSBmyloid precursor protein secretase/CTSB                   | M14221 | 116810 | CYS26ARG                     |  |
| cathepsin B/b-aCTSBmyloid precursor protein                                  | M14221 | 116810 | EcoRI                        |  |

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|                           |         |        |                                 |  |
|---------------------------|---------|--------|---------------------------------|--|
| secretase/CTSB            | M14221  | 116810 | TaqI                            |  |
| cathepsin B/b-aCTSBmyloid |         |        |                                 |  |
| precursor protein         |         |        |                                 |  |
| secretase/CTSB            |         |        |                                 |  |
| Cholecystokinin A         | L13605  | 118444 | GLY21ARG                        |  |
| receptor/CCKAR            | L13605  | 118444 | VAL365ILE                       |  |
| Cholecystokinin A         |         |        |                                 |  |
| receptor/CCKAR            | L08112  | 118445 | 1550 G-->A Val125-->Ile         |  |
| Cholecystokinin B         |         |        |                                 |  |
| receptor/CCKBR            | L08112  | 118445 | CAT 207 CAC His207His           |  |
| Cholecystokinin B         |         |        |                                 |  |
| receptor/CCKBR            | L08112  | 118445 | Arg215His                       |  |
| Cholecystokinin B         |         |        |                                 |  |
| receptor/CCKBR            | L08112  | 118445 | Val138Met                       |  |
| plasma cholesterol        | NM_0000 | 118470 | A1503G                          |  |
| ester transfer            | 78      |        |                                 |  |
| protein/CETP              |         |        |                                 |  |
| plasma cholesterol        | NM_0000 | 118470 | G-A splice junction alternative |  |
| ester transfer            | 78      |        | splice                          |  |
| protein/CETP              |         |        |                                 |  |
| plasma cholesterol        | NM_0000 | 118470 | G1696A                          |  |
| ester transfer            | 78      |        |                                 |  |
| protein/CETP              |         |        |                                 |  |
| plasma cholesterol        | NM_0000 | 118470 | C-T transition in               |  |
| ester transfer            | 78      |        | intron 12                       |  |
| protein/CETP              |         |        |                                 |  |
| plasma cholesterol        | NM_0000 | 118470 | EcoNI                           |  |
| ester transfer            | 78      |        |                                 |  |



|                                                      |               |        |                                             |
|------------------------------------------------------|---------------|--------|---------------------------------------------|
| protein/CETP<br>plasma cholesterol<br>ester transfer | NM_0000<br>78 | 118470 | G-->A intron 14                             |
| protein/CETP<br>plasma cholesterol<br>ester transfer | NM_0000<br>78 | 118470 | G-A transition in<br>intron 15              |
| protein/CETP<br>plasma cholesterol<br>ester transfer | NM_0000<br>78 | 118470 | G1533A                                      |
| protein/CETP<br>plasma cholesterol<br>ester transfer | NM_0000<br>78 | 118470 | INS T alternative<br>(intron/exon14) splice |
| protein/CETP<br>plasma cholesterol<br>ester transfer | NM_0000<br>78 | 118470 | StuI                                        |
| protein/CETP<br>plasma cholesterol<br>ester transfer | NM_0000<br>78 | 118470 | T-->G tyr57stop                             |
| protein/CETP<br>plasma cholesterol<br>ester transfer | NM_0000<br>78 | 118470 | TaqIA                                       |
| protein/CETP<br>plasma cholesterol<br>ester transfer | NM_0000<br>78 | 118470 | TaqIB in intron 1                           |
| protein/CETP<br>plasma cholesterol<br>ester transfer | NM_0000<br>78 | 118470 | 268 Arg--<br>>STOP                          |
| protein/CETP<br>plasma cholesterol<br>ester transfer | NM_0000<br>78 | 118470 | Asp 442 to Gly                              |

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|                                                      |               |        |             |
|------------------------------------------------------|---------------|--------|-------------|
| plasma cholesterol<br>ester transfer<br>protein/CETP | NM_0000<br>78 | 118470 | ASP442GLY   |
| plasma cholesterol<br>ester transfer<br>protein/CETP | NM_0000<br>78 | 118470 | G181X       |
| plasma cholesterol<br>ester transfer<br>protein/CETP | NM_0000<br>78 | 118470 | I405V       |
| plasma cholesterol<br>ester transfer<br>protein/CETP | NM_0000<br>78 | 118470 | Lys309-Stop |
| plasma cholesterol<br>ester transfer<br>protein/CETP | NM_0000<br>78 | 118470 | R451Q       |
| plasma cholesterol<br>ester transfer<br>protein/CETP | NM_0000<br>78 | 118470 | Val421-Ile  |
| Choline<br>acetyltransferase/CHA<br>T                | NM_0030<br>55 | 118490 | none found  |
| Cholinergic Receptor,<br>Muscarinic, 2; CHRM2        | U19800        | 118493 | none found  |
| Cholinergic Receptor,<br>Muscarinic, 3; CHRM3        | U29589        | 118494 | none found  |
| Cholinergic Receptor,<br>Muscarinic, 4; CHRM4        | M16405        | 118495 | SstI        |
| Cholinergic Receptor,<br>Muscarinic, 5; CHRM5        | AF026263      | 118496 | none found  |
| Nicotinic, Cholinergic<br>receptor alpha 2           | U62431        | 118502 | none found  |

|                                               |           |        |                          |  |
|-----------------------------------------------|-----------|--------|--------------------------|--|
| Nicotinic, Cholinergic<br>receptor alpha 3    | X53559    | 118503 | none found               |  |
| Nicotinic, Cholinergic<br>receptor alpha 4    | U62433    | 118504 | 3-BP INS, 776GCT         |  |
| Nicotinic, Cholinergic<br>receptor alpha 4    | U62433    | 118504 | CfoI exon 5              |  |
| Nicotinic, Cholinergic<br>receptor alpha 4    | U62433    | 118504 | Dinucleotide intron<br>1 |  |
| Nicotinic, Cholinergic<br>receptor alpha 4    | U62433    | 118504 | fokI                     |  |
| Nicotinic, Cholinergic<br>receptor alpha 4    | U62433    | 118504 | PvuII                    |  |
| Nicotinic, Cholinergic<br>receptor alpha 4    | U62433    | 118504 | SER-TER                  |  |
| Nicotinic, Cholinergic<br>receptor alpha 4    | U62433    | 118504 | SER248PHE                |  |
| Nicotinic, Cholinergic<br>receptor alpha 5    | M83712    | 118505 | none found               |  |
| Nicotinic, Cholinergic<br>receptor beta 2     | Y08415    | 118507 | none found               |  |
| Nicotinic, Cholinergic<br>receptor beta 3     | X67513    | 118508 | none found               |  |
| Nicotinic, Cholinergic<br>receptor beta 4     | X68275    | 118509 | none found               |  |
| Cholinergic Receptor,<br>Muscarinic, 1; CHRM1 | X15263    | 118510 | none found               |  |
| Nicotinic, Cholinergic<br>receptor alpha 7    | U40583    | 118511 | none found               |  |
| ciliary neurotrophic<br>factor receptor/CNTFR | NM_001842 | 118946 | none found               |  |
| Corticotropin releasing                       | U16273    | 122561 | none found               |  |

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|                      |        |        |                               |   |
|----------------------|--------|--------|-------------------------------|---|
| hormone receptor 1   |        |        |                               |   |
| diazepam binding     | M15887 | 125950 | none found                    |   |
| inhibitor/DBI        |        |        |                               |   |
| Human dihydrofolate  | J00140 | 126060 |                               |   |
| reductase gene       |        |        |                               |   |
| Dopamine Receptor D1 | X58987 | 126449 | C/T Isoleucine49              |   |
| Dopamine Receptor D2 | X51362 | 126450 | 141 C ins/del                 |   |
| Dopamine Receptor D2 | X51362 | 126450 | A241G                         |   |
| Dopamine Receptor D2 | X51362 | 126450 | NcoI RFLP                     |   |
| Dopamine Receptor D2 | X51362 | 126450 | TaqI A, TaqI B,               |   |
|                      |        |        | TaqI D, and (CA) <sub>n</sub> |   |
|                      |        |        | STRP                          |   |
| Dopamine Receptor D2 | X51362 | 126450 | Serine                        |   |
|                      |        |        | 311Cysteine                   |   |
| Dopamine Receptor D3 | U32499 | 126451 | exonic Ball                   |   |
|                      |        |        | polymorphism                  |   |
| Dopamine Receptor D3 | U32499 | 126451 | intronic MspI                 |   |
|                      |        |        | polymorphism                  |   |
| Dopamine Receptor D3 | U32499 | 126451 | Serine9Glycine                |   |
| Dopamine Receptor D4 | L12398 | 126452 | 12 bp                         |   |
|                      |        |        | duplication/deletion          |   |
|                      |        |        | in exon 1                     |   |
| Dopamine Receptor D4 | L12398 | 126452 | 12 bp tandem repeat           |   |
|                      |        |        | in extracellular N-           |   |
|                      |        |        | terminal part of              |   |
|                      |        |        | receptor                      |   |
| Dopamine Receptor D4 | L12398 | 126452 | 12 bp VNTR in exon            | 1 |
| Dopamine Receptor D4 | L12398 | 126452 | 48 bp VNTR in exon            | 3 |
| Dopamine Receptor D4 | L12398 | 126452 | 48 bp VNTR in exon            |   |

|                            |        |        |                                                                          |
|----------------------------|--------|--------|--------------------------------------------------------------------------|
| Dopamine Receptor D4       | L12398 | 126452 | 3<br>48 bp VNTR in exon 3                                                |
| Dopamine Receptor D4       | L12398 | 126452 | 48 bp VNTR in third cytoplasmic loop                                     |
| Dopamine Receptor D4       | L12398 | 126452 | exon 1 -- nondeleted sequence in 13bp deletion site                      |
| Dopamine Receptor D4       | L12398 | 126452 | exon 3 (48 bp repeat)                                                    |
| Dopamine Receptor D4       | L12398 | 126452 | exon 3 (position 194) -- common valine producing T at glycine subst site |
| Dopamine Receptor D4       | L12398 | 126452 | poly G in intron 1                                                       |
| Dopamine Receptor D4       | L12398 | 126452 | SmaI cutting site (bands of 413bp and 302bp) in 5' noncoding region      |
| Dopamine Receptor D4       | L12398 | 126452 | SmaI RFLP in 5' noncoding region                                         |
| Dopamine Receptor D5       | M67439 | 126453 | (TC) <sub>n</sub>                                                        |
| Dopamine Receptor D5       | M67439 | 126453 | dinucleotide repeat                                                      |
| Dopamine Receptor D5       | M67439 | 126453 | poly (CT/GT/GA) <sub>n</sub>                                             |
| Dopamine Receptor D5       | M67439 | 126453 | T978C P326P                                                              |
| Dopamine Receptor D5       | M67439 | 126453 | transmembrane L88F domain II                                             |
| Dopamine Transporter/ DAT1 | L24178 | 126455 | 40-bp VNTR in the 3'-untranslated                                        |
| Dopamine Transporter/ DAT1 | L24178 | 126455 | 5' TaqI RFLP                                                             |

|                                                          |               |        |                                      |
|----------------------------------------------------------|---------------|--------|--------------------------------------|
| Dopamine Transporter/<br>DAT1                            | L24178        | 126455 | 9-repeat allele                      |
| estrogen receptor 1<br>(ESR1)                            | M12674        | 133430 | RFLP (PssI enzyme)                   |
| estrogen receptor 1<br>(ESR1)                            | M12674        | 133430 | RFLP (PvuII<br>enzyme)<br>none found |
| Solute Carrier Family<br>1, Member 1; Slc1a1             | U08989        | 133550 | none found                           |
| Gamma-Aminobutyric<br>Acid Receptor, Alpha-<br>2; Gabra2 | S62907        | 137140 | none found                           |
| Gamma-Aminobutyric<br>Acid Receptor, Alpha-<br>4; Gabra4 | U30461        | 137141 | none found                           |
| Gamma-Aminobutyric<br>Acid Receptor, Alpha-<br>5; Gabra5 | L08485        | 137142 | Dinucleotide repeat                  |
| Gamma-Aminobutyric<br>Acid Receptor, Alpha-<br>6; Gabra6 | S81944        | 137143 | none found                           |
| GABA-glutamate<br>transaminase                           | NM_0006<br>63 | 137150 | 3' DELETION                          |
| GABA-glutamate<br>transaminase                           | NM_0006<br>63 | 137150 | ARG220LYS                            |
| Gamma-Aminobutyric<br>Acid Receptor, Alpha-<br>1; Gabra1 | X14766        | 137160 | Dinucleotide repeat                  |
| Gamma-Aminobutyric<br>Acid Receptor Subunit<br>Rho1      | M62400        | 137161 | PstI                                 |
| Gamma-Aminobutyric                                       | M86868        | 137162 | none found                           |

|                                                 |           |        |                                       |  |  |  |
|-------------------------------------------------|-----------|--------|---------------------------------------|--|--|--|
| Acid Receptor Subunit Rho2                      |           |        |                                       |  |  |  |
| Gamma-Aminobutyric Acid Receptor, Delta;        | AF016917  | 137163 | none found                            |  |  |  |
| Gabrd                                           |           |        |                                       |  |  |  |
| Gamma-Aminobutyric Acid                         | X15376    | 137164 | Ncil                                  |  |  |  |
| Receptor, Gamma-2;                              |           |        |                                       |  |  |  |
| Gabrg2                                          |           |        |                                       |  |  |  |
| Solute carrier family 6 (GABA), member 1/SLC6A1 | X54673    | 137165 | none found                            |  |  |  |
| Gamma-Aminobutyric Acid                         | *****     | 137166 | none found                            |  |  |  |
| Receptor, Gamma-1;                              |           |        |                                       |  |  |  |
| Gabrg1                                          |           |        |                                       |  |  |  |
| Gamma-Aminobutyric Acid Receptor, Beta-1;       | X14767    | 137190 | C-->G his396glu                       |  |  |  |
| Gabrb1                                          |           |        |                                       |  |  |  |
| Gamma-Aminobutyric Acid Receptor, Beta-3;       | M82919    | 137192 | Dinucleotide repeat                   |  |  |  |
| Gabrb3                                          |           |        |                                       |  |  |  |
| glucagon-like peptide 1 receptor/GLP1R          | U01156    | 138032 | silent substitution in exon 6         |  |  |  |
| glucagon-like peptide 1 receptor/GLP1R          | U01156    | 138032 | simple tandem repeat DNA polymorphism |  |  |  |
| glucagon receptor/GCGR                          | NM_000160 | 138033 | Alu-repeat                            |  |  |  |
| glucagon receptor/GCGR                          | NM_000160 | 138033 | GLY40SER                              |  |  |  |

|                        |         |        |                      |           |
|------------------------|---------|--------|----------------------|-----------|
| Glutamate              | X07674  | 138130 | G/A at nt 955        |           |
| dehydrogenase 1        |         |        |                      |           |
| Glutamate              | X07674  | 138130 | TaqI                 |           |
| dehydrogenase 1        |         |        |                      |           |
| Glutamate              | X07674  | 138130 |                      | GLY446ASP |
| dehydrogenase 1        |         |        |                      |           |
| Glutamate              | X07674  | 138130 |                      | GLY446SER |
| dehydrogenase 1        |         |        |                      |           |
| Glutamate              | X07674  | 138130 |                      | HIS454TYR |
| dehydrogenase 1        |         |        |                      |           |
| Glutamate              | X07674  | 138130 |                      | SER445LEU |
| dehydrogenase 1        |         |        |                      |           |
| Glutamate              | X07674  | 138130 |                      | SER448PRO |
| dehydrogenase 1        |         |        |                      |           |
| mitochondrial          | NM_0020 | 138150 | none found           |           |
| glutamate oxaloacetate | 80      |        |                      |           |
| transaminase 2/GOT2    |         |        |                      |           |
| soluble glutamate      | NM_0020 | 138180 | none found           |           |
| oxaloacetate           | 79      |        |                      |           |
| transaminase 1/GOT1    |         |        |                      |           |
| Glutamate Receptor,    | U16127  | 138243 | none found           |           |
| Ionotropic, Kainate 3; |         |        |                      |           |
| Grik3                  |         |        |                      |           |
| Glutamate Receptor,    | S75105  | 138244 | trinucleotide repeat |           |
| Ionotropic, Kainate 2; |         |        | 3'                   |           |
| Grik2                  |         |        |                      |           |
| Glutamate Receptor,    | U16125  | 138245 | none found           |           |
| Ionotropic, Kainate 1; |         |        |                      |           |
| Grik1                  |         |        |                      |           |
| Glutamate Receptor,    | NM_0008 | 138246 | none found           |           |
| Ionotropic, Ampa 4;    | 29      |        |                      |           |



|                                                                  |        |        |                             |
|------------------------------------------------------------------|--------|--------|-----------------------------|
| Gria4                                                            | L20814 | 138247 | none found                  |
| Glutamate Receptor,<br>Ionotropic, Ampa 2;                       |        |        |                             |
| Gria2                                                            | M64752 | 138248 | none found                  |
| Glutamate Receptor,<br>Ionotropic, Ampa 1;                       |        |        |                             |
| Gria1                                                            | L13266 | 138249 | none found                  |
| Glutamate Receptor,<br>Ionotropic, N-Methyl-<br>D-Asp 1; Grin1   |        |        |                             |
| Glutamate Receptor,<br>Ionotropic, N-Methyl-<br>D-Asp A; Grina   | *****  | 138251 | none found                  |
| Glutamate Receptor,<br>Ionotropic, N-Methyl-<br>D-Asp 2b; Grin2b | U28758 | 138252 | none found                  |
| Glutamate Receptor,<br>Ionotropic, N-Methyl-<br>D-Asp 2a; Grin2a | U09002 | 138253 | none found                  |
| Glutamate Receptor,<br>Ionotropic, N-Methyl-<br>D-Asp 2c; Grin2c | L76224 | 138254 | none found                  |
| Glutamate<br>decarboxylase 2 (brain,<br>65kD)                    | X69936 | 138275 | (CA) repeat<br>polymorphism |
| Glutamate<br>decarboxylase 3                                     |        | 138276 | none found                  |
| Glycine Receptor,<br>Alpha-1 Subunit; Glra1                      | X52009 | 138491 | null allele                 |
| Glycine Receptor,<br>Alpha-1 Subunit; Glra1                      | X52009 | 138491 | ARG271GLN                   |

|                                                                                     |               |        |            |
|-------------------------------------------------------------------------------------|---------------|--------|------------|
| Glycine Receptor,<br>Alpha-1 Subunit; Glra1                                         | X52009        | 138491 | ARG271LEU  |
| Glycine Receptor,<br>Alpha-1 Subunit; Glra1                                         | X52009        | 138491 | GLN266HIS  |
| Glycine Receptor,<br>Alpha-1 Subunit; Glra1                                         | X52009        | 138491 | ILE244ASN  |
| Glycine Receptor,<br>Alpha-1 Subunit; Glra1                                         | X52009        | 138491 | LYS276GLU  |
| Glycine Receptor,<br>Alpha-1 Subunit; Glra1                                         | X52009        | 138491 | P250T      |
| Glycine Receptor,<br>Alpha-1 Subunit; Glra1                                         | X52009        | 138491 | TYR279CYS  |
| Glycine Receptor, Beta<br>Subunit; Glrb                                             | U33267        | 138492 | none found |
| gonadotropin releasing<br>hormone receptor/G<br>protein-<br>coupled/LHRHR/GNR<br>HR | NM_0004<br>06 | 138850 | ARG262GLN  |
| gonadotropin releasing<br>hormone receptor/G<br>protein-<br>coupled/LHRHR/GNR<br>HR | NM_0004<br>06 | 138850 | GLN106ARG  |
| gonadotropin releasing<br>hormone receptor/G<br>protein-<br>coupled/LHRHR/GNR<br>HR | NM_0004<br>06 | 138850 | Mae III    |
| gonadotropin releasing<br>hormone receptor/G                                        | NM_0004<br>06 | 138850 | TYR284CYS  |

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|                                                                   |        |        |                                    |
|-------------------------------------------------------------------|--------|--------|------------------------------------|
| protein-coupled/LHRHR/GNRHR                                       | U34195 | 139191 | IVS8DS, G-C, -1 alternative splice |
| growth hormone releasing hormone receptor/G protein-coupled/GHRHR | U34195 | 139191 | 1-BP DEL frameshift                |
| growth hormone releasing hormone receptor/G protein-coupled/GHRHR | U34195 | 139191 | 2-BP DEL frameshift                |
| growth hormone releasing hormone receptor/G protein-coupled/GHRHR | U34195 | 139191 | C to T codon 236. silent           |
| growth hormone releasing hormone receptor/G protein-coupled/GHRHR | U34195 | 139191 | EX4,6DEL                           |
| growth hormone releasing hormone receptor/G protein-coupled/GHRHR | U34195 | 139191 | GAA180GAG silent                   |
| growth hormone releasing hormone receptor/G protein-coupled/GHRHR | U34195 | 139191 | IVS4DS, G-A, +1 alternative splice |

|                                                                             |        |        |                            |
|-----------------------------------------------------------------------------|--------|--------|----------------------------|
| growth hormone<br>releasing hormone<br>receptor/G protein-<br>coupled/GHRHR | U34195 | 139191 | IVS6AS, G-T, -1            |
| growth hormone<br>releasing hormone<br>receptor/G protein-<br>coupled/GHRHR | U34195 | 139191 | IVS8AS, G-C, -1            |
| growth hormone<br>releasing hormone<br>receptor/G protein-<br>coupled/GHRHR | U34195 | 139191 | IVS9DS, G-A, +1 frameshift |
| growth hormone<br>releasing hormone<br>receptor/G protein-<br>coupled/GHRHR | U34195 | 139191 | P561T                      |
| growth hormone<br>releasing hormone<br>receptor/G protein-<br>coupled/GHRHR | U34195 | 139191 | ARG161CYS                  |
| growth hormone<br>releasing hormone<br>receptor/G protein-<br>coupled/GHRHR | U34195 | 139191 | ARG217TER                  |
| growth hormone<br>releasing hormone<br>receptor/G protein-<br>coupled/GHRHR | U34195 | 139191 | ARG43TER                   |
| growth hormone<br>releasing hormone<br>receptor/G protein-<br>coupled/GHRHR | U34195 | 139191 | ASP152HIS                  |

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|                                                                                              |        |        |           |
|----------------------------------------------------------------------------------------------|--------|--------|-----------|
| coupled/GHRHR<br>growth hormone<br>releasing hormone<br>receptor/G protein-<br>coupled/GHRHR | U34195 | 139191 | CYS38TER  |
| growth hormone<br>releasing hormone<br>receptor/G protein-<br>coupled/GHRHR                  | U34195 | 139191 | GLN154PRO |
| growth hormone<br>releasing hormone<br>receptor/G protein-<br>coupled/GHRHR                  | U34195 | 139191 | GLU224ASP |
| growth hormone<br>releasing hormone<br>receptor/G protein-<br>coupled/GHRHR                  | U34195 | 139191 | GLU224TER |
| growth hormone<br>releasing hormone<br>receptor/G protein-<br>coupled/GHRHR                  | U34195 | 139191 | GLU44LYS  |
| growth hormone<br>releasing hormone<br>receptor/G protein-<br>coupled/GHRHR                  | U34195 | 139191 | ILE153THR |
| growth hormone<br>releasing hormone<br>receptor/G protein-<br>coupled/GHRHR                  | U34195 | 139191 | PHE96SER  |
| growth hormone<br>releasing hormone<br>receptor/G protein-<br>coupled/GHRHR                  | U34195 | 139191 | PRO131GLN |

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|                                                                                                                                                                      |           |        |                                      |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------|--------|--------------------------------------|
| receptor/G protein-coupled/GHRHR growth hormone releasing hormone receptor/G protein-coupled/GHRHR growth hormone releasing hormone receptor/G protein-coupled/GHRHR | U34195    | 139191 | VAL144ILE                            |
| growth hormone releasing hormone receptor/G protein-coupled/GHRHR                                                                                                    | U34195    | 139191 | VAL155GLY                            |
| Histamine receptor H2                                                                                                                                                | M64799    | 142703 | A649G                                |
| Histidine                                                                                                                                                            | M60445    | 142704 | none found                           |
| Decarboxylase                                                                                                                                                        |           |        |                                      |
| HMGCoA reductase/HMGCR                                                                                                                                               | NM_000859 | 142910 | HgiAI                                |
| HMGCoA reductase/HMGCR                                                                                                                                               | NM_000859 | 142910 | ScrFI polymorphism in the 2nd intron |
| Superoxide Dismutase 1/SOD1 (soluble)                                                                                                                                | NM_000454 | 147450 | T-G, -10, 9-BP INS                   |
| Superoxide Dismutase 1/SOD1 (soluble)                                                                                                                                | NM_000454 | 147450 | VS4AS, A-G, -11                      |
| Superoxide Dismutase 1/SOD1 (soluble)                                                                                                                                | NM_000454 | 147450 | ALA145THR                            |
| Superoxide Dismutase 1/SOD1 (soluble)                                                                                                                                | NM_000454 | 147450 | ALA4THR                              |
| Superoxide Dismutase 1/SOD1 (soluble)                                                                                                                                | NM_000454 | 147450 | ALA4VAL                              |
| Superoxide Dismutase 1/SOD1 (soluble)                                                                                                                                | NM_000454 | 147450 | ASP90ALA                             |
| Superoxide Dismutase 1/SOD1 (soluble)                                                                                                                                | NM_000454 | 147450 | CYS6PHE                              |

|                                          |               |        |           |
|------------------------------------------|---------------|--------|-----------|
| Superoxide Dismutase<br>1/SOD1 (soluble) | NM_0004<br>54 | 147450 | GLU100GLY |
| Superoxide Dismutase<br>1/SOD1 (soluble) | NM_0004<br>54 | 147450 | GLU21LYS  |
| Superoxide Dismutase<br>1/SOD1 (soluble) | NM_0004<br>54 | 147450 | GLY16SER  |
| Superoxide Dismutase<br>1/SOD1 (soluble) | NM_0004<br>54 | 147450 | GLY37ARG  |
| Superoxide Dismutase<br>1/SOD1 (soluble) | NM_0004<br>54 | 147450 | GLY41ASP  |
| Superoxide Dismutase<br>1/SOD1 (soluble) | NM_0004<br>54 | 147450 | GLY41SER  |
| Superoxide Dismutase<br>1/SOD1 (soluble) | NM_0004<br>54 | 147450 | GLY72SER  |
| Superoxide Dismutase<br>1/SOD1 (soluble) | NM_0004<br>54 | 147450 | GLY85ARG  |
| Superoxide Dismutase<br>1/SOD1 (soluble) | NM_0004<br>54 | 147450 | GLY93ALA  |
| Superoxide Dismutase<br>1/SOD1 (soluble) | NM_0004<br>54 | 147450 | GLY93CYS  |
| Superoxide Dismutase<br>1/SOD1 (soluble) | NM_0004<br>54 | 147450 | HIS43ARG  |
| Superoxide Dismutase<br>1/SOD1 (soluble) | NM_0004<br>54 | 147450 | HIS46ARG  |
| Superoxide Dismutase<br>1/SOD1 (soluble) | NM_0004<br>54 | 147450 | ILE104THE |
| Superoxide Dismutase<br>1/SOD1 (soluble) | NM_0004<br>54 | 147450 | ILE113THR |
| Superoxide Dismutase<br>1/SOD1 (soluble) | NM_0004<br>54 | 147450 | LEU106VAL |
| Superoxide Dismutase<br>1/SOD1 (soluble) | NM_0004<br>54 | 147450 | LEU126TER |

|                      |         |        |  |  |                  |
|----------------------|---------|--------|--|--|------------------|
| 1/SOD1 (soluble)     | 54      |        |  |  | LEU144SER        |
| Superoxide Dismutase | NM_0004 | 147450 |  |  |                  |
| 1/SOD1 (soluble)     | 54      |        |  |  | LEU38VAL         |
| Superoxide Dismutase | NM_0004 | 147450 |  |  |                  |
| 1/SOD1 (soluble)     | 54      |        |  |  | LEU84VAL         |
| Superoxide Dismutase | NM_0004 | 147450 |  |  |                  |
| 1/SOD1 (soluble)     | 54      |        |  |  | SER134ASN        |
| Superoxide Dismutase | NM_0004 | 147450 |  |  |                  |
| 1/SOD1 (soluble)     | 54      |        |  |  | THR151ILE        |
| Superoxide Dismutase | NM_0004 | 147450 |  |  | Val7-->Glu       |
| 1/SOD1 (soluble)     | 54      |        |  |  |                  |
| Superoxide dismutase | X02317  | 147450 |  |  |                  |
| 1 (Cu/Zn)            |         |        |  |  |                  |
| Superoxide Dismutase | X65965  | 147460 |  |  | ALA16VAL         |
| 2/SOD2               |         |        |  |  |                  |
| (mitochondrial)      |         |        |  |  |                  |
| Human clone pSK1     | U05875  | 147569 |  |  | Gln64Arg         |
| interferon gamma     |         |        |  |  |                  |
| receptor accessory   |         |        |  |  |                  |
| factor-1 (AF-1)      |         |        |  |  |                  |
| mRNA, complete cds   |         |        |  |  |                  |
| MICROTUBULE-         | J03778  | 157140 |  |  | +39deltaG iron 4 |
| ASSOCIATED           |         |        |  |  |                  |
| PROTEIN TAU          |         |        |  |  |                  |
| MICROTUBULE-         | J03778  | 157140 |  |  | IVS10, A-G, +13  |
| ASSOCIATED           |         |        |  |  |                  |
| PROTEIN TAU          |         |        |  |  |                  |
| MICROTUBULE-         | J03778  | 157140 |  |  | IVS10, C-U, +14  |
| ASSOCIATED           |         |        |  |  |                  |



|                                   |           |        |                 |           |
|-----------------------------------|-----------|--------|-----------------|-----------|
| PROTEIN TAU                       | J03778    | 157140 | IVS10, C-U, +16 |           |
| MICROTUBULE-ASSOCIATED            |           |        |                 |           |
| PROTEIN TAU                       | J03778    | 157140 | IVS10, G-A, +1  |           |
| MICROTUBULE-ASSOCIATED            |           |        |                 |           |
| PROTEIN TAU                       | J03778    | 157140 |                 | ARG406TRP |
| MICROTUBULE-ASSOCIATED            |           |        |                 |           |
| PROTEIN TAU                       | J03778    | 157140 |                 | ASN279LYS |
| MICROTUBULE-ASSOCIATED            |           |        |                 |           |
| PROTEIN TAU                       | J03778    | 157140 |                 | GLY272VAL |
| MICROTUBULE-ASSOCIATED            |           |        |                 |           |
| PROTEIN TAU                       | J03778    | 157140 |                 | PRO301LEU |
| MICROTUBULE-ASSOCIATED            |           |        |                 |           |
| PROTEIN TAU                       | J03778    | 157140 |                 | SER305ASN |
| MICROTUBULE-ASSOCIATED            |           |        |                 |           |
| PROTEIN TAU                       | J03778    | 157140 |                 | VAL337MET |
| MICROTUBULE-ASSOCIATED            |           |        |                 |           |
| nerve growth factor receptor/NGFR | NM_002507 | 162010 |                 | HincII    |
| nerve growth factor receptor/NGFR | NM_002507 | 162010 |                 | HindIII   |
| nerve growth factor receptor/NGFR | NM_002507 | 162010 | Two TaqI sites  |           |

|                                                             |               |        |                           |           |
|-------------------------------------------------------------|---------------|--------|---------------------------|-----------|
| nerve growth factor<br>receptor/NGFR                        | NM_0025<br>07 | 162010 | XmnI                      |           |
| H.sapiens encoding<br>PC1/PC3                               | X64810        | 162150 | IVS5DS, A-C, +4           |           |
| H.sapiens encoding<br>PC1/PC3                               | X64810        | 162150 |                           | GLY483ARG |
| Tachykinin NK2<br>receptor/TACR2                            | M57414        | 162321 | none found                |           |
| Tachykinin NK1<br>receptor/TACR1                            | M81797        | 162323 | none found                |           |
| Tachykinin NK3<br>receptor/TACR3                            | M89473        | 162332 | none found                |           |
| neuromedin B<br>receptor/g protein-<br>coupled/NMBR         | *****         | 162341 | none found                |           |
| Neuropeptide Y                                              | K01911        | 162640 |                           | LEU7PRO   |
| Neuropeptide Y<br>receptor Y1/NPY1R                         | M84755        | 162641 | none found                |           |
| Neuropeptide Y<br>receptor Y2/NPY2R                         | U32500        | 162642 | none found                |           |
| Neuropeptide Y<br>receptor Y3/chemokine<br>receptor 4/CXCR4 | X71635        | 162643 | none found                |           |
| Neurotensin receptor                                        | X70070        | 162651 | Tetranucleotide<br>repeat |           |
| Human AD amyloid<br>mRNA, complete cds                      | L08850        | 163890 | Dinucleotide repeat       |           |
| Human AD amyloid<br>mRNA, complete cds                      | L08850        | 163890 |                           | ALA30PRO  |
| Human AD amyloid<br>mRNA, complete cds                      | L08850        | 163890 |                           | ALA53THR  |

|                                                           |         |        |                            |
|-----------------------------------------------------------|---------|--------|----------------------------|
| Human AD amyloid<br>mRNA, complete cds                    | L08850  | 163890 | G209A                      |
| Solute carrier family 6,<br>member 43                     | NM_0010 | 163970 | none found                 |
| 5/SLC6A2/NAT1/NET<br>1 (glycine)                          |         |        |                            |
| Human obese (ob)                                          | U18915  | 164160 | -1387 G/A                  |
| mRNA, complete cds                                        |         |        |                            |
| Human obese (ob)                                          | U18915  | 164160 | 1-BP DEL frameshift        |
| mRNA, complete cds                                        |         |        |                            |
| Human obese (ob)                                          | U18915  | 164160 | A --> G + 19 exon1         |
| mRNA, complete cds                                        |         |        |                            |
| Human obese (ob)                                          | U18915  | 164160 | C(-188)A                   |
| mRNA, complete cds                                        |         |        |                            |
| Human obese (ob)                                          | U18915  | 164160 | ARG105TRP                  |
| mRNA, complete cds                                        |         |        |                            |
| Human obese (ob)                                          | U18915  | 164160 | Glu-126-Gln                |
| mRNA, complete cds                                        |         |        |                            |
| Human obese (ob)                                          | U18915  | 164160 | Ser-91-Ser                 |
| mRNA, complete cds                                        |         |        |                            |
| Opioid Receptor,<br>Delta-1; Oprd1                        | U10504  | 165195 | T to C in codon 307 silent |
| Opioid Receptor,<br>Kappa-1; Oprk1                        | U17298  | 165196 | none found                 |
| Oxytocin receptor                                         | X64878  | 167055 | C to T exon 3              |
| Oxytocin receptor                                         | X64878  | 167055 | CA repeat                  |
| Human peptidylglycine<br>alpha-amidating<br>monooxygenase | M37721  | 170270 | none found                 |
| mRNA, complete cds                                        |         |        |                            |
| Phenol-preferring                                         | NM_0010 | 171150 | Arg213His                  |

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|                                                      |           |        |                           |           |
|------------------------------------------------------|-----------|--------|---------------------------|-----------|
| sulfotransferase, family 1A, member 1/SLIT1A1        | 55        |        |                           |           |
| phenylethanolamine N-methyltransferase/PNMT          | NM_002686 | 171190 | BANI                      |           |
| phospholipid transfer protein/PLTP                   | NM_006227 | 172425 | TaqIB                     |           |
| Methenyltetrahydrofolate cyclohydrolase              | J04031    | 172460 |                           | ARG293HIS |
| prolactin receptor/PRLR                              | NM_000949 | 176761 | none found                |           |
| Adrenocorticotrophic hormone (ACTH)                  | M28636    | 176830 | 3804C-A                   |           |
| Adrenocorticotrophic hormone (ACTH)                  | M28636    | 176830 | 7013G-T                   |           |
| Adrenocorticotrophic hormone (ACTH)                  | M28636    | 176830 | 7133C DEL                 |           |
| butyrylcholinesterase 1/serum cholinesterase 1/BCHE1 | NM_000055 | 177400 | 209 A/G Asp-70 to Gly     |           |
| butyrylcholinesterase 1/serum cholinesterase 1/BCHE1 | NM_000055 | 177400 | 342-bp Alu in exon two    |           |
| butyrylcholinesterase 1/serum cholinesterase 1/BCHE1 | NM_000055 | 177400 | A-to-G Y128C              |           |
| butyrylcholinesterase 1/serum cholinesterase 1/BCHE1 | NM_000055 | 177400 | GCA to ACA ALA539THR      |           |
| butyrylcholinesterase 1/BCHE1                        | NM_000055 | 177400 | GGT to GTT Gly 390 to Val |           |

|                        |         |        |                     |  |
|------------------------|---------|--------|---------------------|--|
| 1/serum cholinesterase | 55      |        |                     |  |
| 1/B <sub>0</sub> HEI   |         |        |                     |  |
| butyrylcholinesterase  | NM_0000 | 177400 | GGT-to-GGAG Gly 117 |  |
| 1/serum cholinesterase | 55      |        | Frameshift          |  |
| 1/B <sub>0</sub> HEI   |         |        |                     |  |
| butyrylcholinesterase  | NM_0000 | 177400 | E451X               |  |
| 1/serum cholinesterase | 55      |        |                     |  |
| 1/B <sub>0</sub> HEI   |         |        |                     |  |
| butyrylcholinesterase  | NM_0000 | 177400 | F446V               |  |
| 1/serum cholinesterase | 55      |        |                     |  |
| 1/B <sub>0</sub> HEI   |         |        |                     |  |
| butyrylcholinesterase  | NM_0000 | 177400 | G365R               |  |
| 1/serum cholinesterase | 55      |        |                     |  |
| 1/B <sub>0</sub> HEI   |         |        |                     |  |
| butyrylcholinesterase  | NM_0000 | 177400 | GLU497VAL           |  |
| 1/serum cholinesterase | 55      |        |                     |  |
| 1/B <sub>0</sub> HEI   |         |        |                     |  |
| butyrylcholinesterase  | NM_0000 | 177400 | Gly115 by Asp       |  |
| 1/serum cholinesterase | 55      |        |                     |  |
| 1/B <sub>0</sub> HEI   |         |        |                     |  |
| butyrylcholinesterase  | NM_0000 | 177400 | LEU330ILE           |  |
| 1/serum cholinesterase | 55      |        |                     |  |
| 1/B <sub>0</sub> HEI   |         |        |                     |  |
| butyrylcholinesterase  | NM_0000 | 177400 | Q119X               |  |
| 1/serum cholinesterase | 55      |        |                     |  |
| 1/B <sub>0</sub> HEI   |         |        |                     |  |
| butyrylcholinesterase  | NM_0000 | 177400 | R515C               |  |
| 1/serum cholinesterase | 55      |        |                     |  |
| 1/B <sub>0</sub> HEI   |         |        |                     |  |
| butyrylcholinesterase  | NM_0000 | 177400 | THR243MET           |  |
| 1/serum cholinesterase | 55      |        |                     |  |

|                        |         |        |                            |           |
|------------------------|---------|--------|----------------------------|-----------|
| 1/B <sub>0</sub> HE1   |         |        |                            | THR250PRO |
| butyrylcholinesterase  | NM_0000 | 177400 |                            |           |
| 1/serum cholinesterase | 55      |        |                            |           |
| 1/B <sub>0</sub> HE1   |         |        |                            |           |
| butyrylcholinesterase  | NM_0000 | 177400 |                            |           |
| 1/serum cholinesterase | 55      |        |                            |           |
| 1/B <sub>0</sub> HE1   |         |        |                            |           |
| butyrylcholinesterase  | *****   | 177500 | none found                 |           |
| 2/serum cholinesterase |         |        |                            |           |
| 2/B <sub>0</sub> HE2   |         |        |                            |           |
| retinoic acid receptor | M57707  | 180190 | none found                 |           |
| gamma/RARG             |         |        |                            |           |
| retinoic acid receptor | NM_0009 | 180220 | none found                 |           |
| beta RARB              | 65      |        |                            |           |
| retinoic acid receptor | NM_0009 | 180240 | 7-base deletion frameshift |           |
| alpha/RARA             | 64      |        |                            |           |
| retinoic acid receptor | NM_0009 | 180240 | codon 411 C to T           |           |
| alpha/RARA             | 64      |        |                            | Arg272Gln |
| retinoic acid receptor | NM_0009 | 180240 |                            | Met297Leu |
| alpha/RARA             | 64      |        |                            |           |
| retinoic acid receptor | NM_0009 | 180245 | none found                 |           |
| retinoid X receptor    | 57      |        |                            |           |
| alpha/RXRA             |         |        |                            |           |
| retinoid X receptor    | X66424  | 180246 | none found                 |           |
| beta RXRB              |         |        |                            |           |
| retinoid X receptor    | U38480  | 180247 | none found                 |           |
| gamma/RXRG             |         |        |                            |           |
| serotonin 5-HT         | M81590  | 182131 | C129T                      |           |
| receptors 5-HT1B, G    |         |        |                            |           |
| protein-coupled        |         |        |                            |           |

|                                                          |        |        |                           |  |
|----------------------------------------------------------|--------|--------|---------------------------|--|
| serotonin 5-HT<br>receptors 5-HT1B, G<br>protein-coupled | M81590 | 182131 | G861C                     |  |
| serotonin 5-HT<br>receptors 5-HT1E, G<br>protein-coupled | M91467 | 182132 | none found                |  |
| serotonin 5-HT<br>receptors 5-HT1D, G<br>protein-coupled | M81590 | 182133 | silent<br>polymorphism    |  |
| serotonin 5-HT<br>receptors 5-HT1F, G<br>protein-coupled | L05597 | 182134 | none found                |  |
| serotonin 5-HT<br>receptors 5-HT2A, G<br>protein-coupled | D87030 | 182135 | -1438G/A.                 |  |
| serotonin 5-HT<br>receptors 5-HT2A, G<br>protein-coupled | D87030 | 182135 | 102T-C                    |  |
| serotonin 5-HT<br>receptors 5-HT2A, G<br>protein-coupled | D87030 | 182135 | HpaII                     |  |
| serotonin 5-HT<br>receptors 5-HT2A, G<br>protein-coupled | D87030 | 182135 | His452Tyr                 |  |
| serotonin 5-HT<br>receptors 5-HT7, G<br>protein-coupled  | L21195 | 182137 | none found                |  |
| serotonin transporter                                    | X70697 | 182138 | PstI                      |  |
| serotonin transporter                                    | X70697 | 182138 | promoter 44-bp<br>ins/del |  |
| serotonin transporter                                    | X70697 | 182138 | tandem repeat close       |  |

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|                                                                          |        |        |                                                 |
|--------------------------------------------------------------------------|--------|--------|-------------------------------------------------|
| serotonin transporter                                                    | X70697 | 182138 | to the promoter<br>two polyadenylation<br>sites |
| serotonin transporter                                                    | X70697 | 182138 | VNTR intron 2                                   |
| serotonin transporter                                                    | X70697 | 182138 | silent<br>polymorphism                          |
| serotonin 5-HT<br>receptors 5-HT3, gated<br>ion channel                  | D49394 | 182139 | none found                                      |
| type I voltage<br>dependent sodium<br>channel alpha<br>subunit/SCN1A     | S71446 | 182389 | none found                                      |
| type II voltage<br>dependent sodium<br>channel alpha 1<br>subunit/SCN2A1 | M94055 | 182390 | none found                                      |
| type III voltage<br>dependent sodium<br>channel alpha<br>subunit/SCN3A   | S69887 | 182391 | none found                                      |
| type VI voltage<br>dependent sodium<br>channel alpha<br>subunit/SCN6A    | M55662 | 182392 | none found                                      |
| Somatostatin receptor<br>1/G protein-coupled                             | M81829 | 182451 | (CA) <sub>n</sub> 5'                            |
| Somatostatin receptor 2                                                  | M81830 | 182452 | TRP188TER                                       |
| Somatostatin receptor<br>3/adrenyl cyclase<br>coupled                    | M96738 | 182453 | none found                                      |

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|                                                               |        |        |                                    |           |
|---------------------------------------------------------------|--------|--------|------------------------------------|-----------|
| Somatostatin receptor 4                                       | L07833 | 182454 | none found                         |           |
| Somatostatin receptor 5                                       | D16827 | 182455 | 2 RFLP's promoter                  |           |
| Human rapamycin-binding protein (FKBP-1) mRNA, complete cds   | M65128 | 186946 | none found                         |           |
| thyrotropin releasing hormone receptor/G protein coupled/TRHR | X75071 | 188545 | 9-BP DEL deletion of 3 amino acids |           |
| thyrotropin releasing hormone receptor/G protein coupled/TRHR | X75071 | 188545 |                                    | ALA118THR |
| thyrotropin releasing hormone receptor/G protein coupled/TRHR | X75071 | 188545 |                                    | ARG171TER |
| oncogene NM_001982 ERBB3/HER3                                 |        | 190151 | none found                         |           |
| tryptophan Hydroxylase; TPH                                   | X52836 | 191060 | -5806G>T                           |           |
| tryptophan Hydroxylase; TPH                                   | X52836 | 191060 | -6526A>G                           |           |
| tryptophan Hydroxylase; TPH                                   | X52836 | 191060 | -7065C>T                           |           |
| tryptophan Hydroxylase; TPH                                   | X52836 | 191060 | 7180T>G                            |           |
| tryptophan Hydroxylase; TPH                                   | X52836 | 191060 | A218C in intron 7                  |           |
| tryptophan Hydroxylase; TPH                                   | X52836 | 191060 | A779C                              |           |
| tryptophan Hydroxylase; TPH                                   | X52836 | 191060 | A779C in intron 7                  |           |

|                       |        |        |                            |
|-----------------------|--------|--------|----------------------------|
| tryptophan            | X52836 | 191060 | T1095C                     |
| Hydroxylase; TPH      |        |        |                            |
| Human tryptophan      | U32989 | 191070 | 6G->T intron               |
| oxygenase (TDO)       |        |        |                            |
| mRNA, complete cds    |        |        |                            |
| Human tryptophan      | U32989 | 191070 | CCCCCT repeat              |
| oxygenase (TDO)       |        |        |                            |
| mRNA, complete cds    |        |        |                            |
| Human tryptophan      | U32989 | 191070 | GTT repeat                 |
| oxygenase (TDO)       |        |        |                            |
| mRNA, complete cds    |        |        |                            |
| tyrosine Hydroxylase  | X05290 | 191290 | (TCAT)n intron 1           |
| tyrosine Hydroxylase  | X05290 | 191290 | BglII                      |
| tyrosine Hydroxylase  | X05290 | 191290 | DraI                       |
| tyrosine Hydroxylase  | X05290 | 191290 | PstI                       |
| tyrosine Hydroxylase  | X05290 | 191290 | ScaI                       |
| tyrosine Hydroxylase  | X05290 | 191290 | T-229A                     |
| tyrosine Hydroxylase  | X05290 | 191290 | [AATG]n                    |
| tyrosine Hydroxylase  | X05290 | 191290 | ARG233HIS                  |
| tyrosine Hydroxylase  | X05290 | 191290 | GLN381LYS                  |
| tyrosine Hydroxylase  | X05290 | 191290 | LEU205PRO                  |
| tyrosine Hydroxylase  | X05290 | 191290 | Val468Met                  |
| tyrosine Hydroxylase  | X05290 | 191290 | Val81Met                   |
| neurotrophic tyrosine | Y09033 | 191315 | 1-BP DEL, 1726C frameshift |
| kinase receptor type  |        |        |                            |
| 1/NTRK1               |        |        |                            |
| neurotrophic tyrosine | Y09033 | 191315 | 1810C>T                    |
| kinase receptor type  |        |        |                            |
| 1/NTRK1               |        |        |                            |
| neurotrophic tyrosine | Y09033 | 191315 | 1838G>T                    |
| kinase receptor type  |        |        |                            |

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|                                                  |               |        |                     |  |
|--------------------------------------------------|---------------|--------|---------------------|--|
| Vesicular Amine<br>Transporter 2; VAT2           | L09118        | 193001 | TaqI                |  |
| Vesicular Amine<br>Transporter 1; VAT1           | *****         | 193002 | none found          |  |
| melanocortin 2<br>receptor/ACTH                  | NM_0005<br>29 | 202200 | 1-BP INS frameshift |  |
| receptor/MC2R<br>melanocortin 2<br>receptor/ACTH | NM_0005<br>29 | 202200 | ARG128CYS           |  |
| receptor/MC2R<br>melanocortin 2<br>receptor/ACTH | NM_0005<br>29 | 202200 | ARG201TER           |  |
| receptor/MC2R<br>melanocortin 2<br>receptor/ACTH | NM_0005<br>29 | 202200 | ASP107ASN           |  |
| receptor/MC2R<br>melanocortin 2<br>receptor/ACTH | NM_0005<br>29 | 202200 | CYS251PHE           |  |
| receptor/MC2R<br>melanocortin 2<br>receptor/ACTH | NM_0005<br>29 | 202200 | SER120ARG           |  |
| receptor/MC2R<br>melanocortin 2<br>receptor/ACTH | NM_0005<br>29 | 202200 | SER74ILE            |  |
| dopamine beta<br>hydroxylase                     | Y00096        | 223360 |                     |  |
| glutamate<br>formiminotransferase/d              | *****         | 229100 | none found          |  |
| ihydrofolate synthetase<br>5,10-                 | U09806        | 236250 | 1027T-G             |  |

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|                                                      |        |        |                    |
|------------------------------------------------------|--------|--------|--------------------|
| @METHYLENETET<br>RAHYDROFOLATE<br>REDUCTASE<br>5,10- | U09806 | 236250 | 1084C-T            |
| @METHYLENETET<br>RAHYDROFOLATE<br>REDUCTASE<br>5,10- | U09806 | 236250 | 1298A-C            |
| @METHYLENETET<br>RAHYDROFOLATE<br>REDUCTASE<br>5,10- | U09806 | 236250 | 1711C-T            |
| @METHYLENETET<br>RAHYDROFOLATE<br>REDUCTASE<br>5,10- | U09806 | 236250 | 677C-T ala --> val |
| @METHYLENETET<br>RAHYDROFOLATE<br>REDUCTASE<br>5,10- | U09806 | 236250 | 983A-G             |
| @METHYLENETET<br>RAHYDROFOLATE<br>REDUCTASE<br>5,10- | U09806 | 236250 | exon 7 Ala-->Glu   |
| @METHYLENETET<br>RAHYDROFOLATE<br>REDUCTASE<br>5,10- | U09806 | 236250 | A225V              |

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|                                                      |        |        |                       |
|------------------------------------------------------|--------|--------|-----------------------|
| 5,10-<br>@METHYLENETET<br>RAHYDROFOLATE<br>REDUCTASE | U09806 | 236250 | ARG158GLN             |
| 5,10-<br>@METHYLENETET<br>RAHYDROFOLATE<br>REDUCTASE | U09806 | 236250 | ARG184TER             |
| Glycine cleavage<br>system: Protein T                | D13811 | 238310 | 1-BP DEL, 183C        |
| Glycine cleavage<br>system: Protein T                | D13811 | 238310 | ASP276HIS             |
| Glycine cleavage<br>system: Protein T                | D13811 | 238310 | GLY269ASP             |
| Glycine cleavage<br>system: Protein T                | D13811 | 238310 | GLY47ARG              |
| Glycine cleavage<br>system: Protein T                | D13811 | 238310 | HIS42ARG              |
| 6-pyruvoyl<br>tetrahydrobiopterin<br>synthase/PTPS   | Q03393 | 261640 | 14-BP DEL K120-->Stop |
| 6-pyruvoyl<br>tetrahydrobiopterin<br>synthase/PTPS   | Q03393 | 261640 | ARG16CYS              |
| 6-pyruvoyl<br>tetrahydrobiopterin<br>synthase/PTPS   | Q03393 | 261640 | ARG25GLN              |
| 6-pyruvoyl<br>tetrahydrobiopterin<br>synthase/PTPS   | Q03393 | 261640 | ASN47ASP              |
| 6-pyruvoyl<br>tetrahydrobiopterin<br>synthase/PTPS   | Q03393 | 261640 | ASN52SER              |

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|                                                                                                    |        |        |            |
|----------------------------------------------------------------------------------------------------|--------|--------|------------|
| tetrahydrobiopterin<br>synthase/PTPS<br>6-pyruvoyl                                                 | Q03393 | 261640 | ASP116GLY  |
| tetrahydrobiopterin<br>synthase/PTPS<br>6-pyruvoyl                                                 | Q03393 | 261640 | ASP96ASN   |
| tetrahydrobiopterin<br>synthase/PTPS<br>6-pyruvoyl                                                 | Q03393 | 261640 | D136V      |
| tetrahydrobiopterin<br>synthase/PTPS<br>6-pyruvoyl                                                 | Q03393 | 261640 | K129E      |
| tetrahydrobiopterin<br>synthase/PTPS<br>6-pyruvoyl                                                 | Q03393 | 261640 | PRO87SER   |
| tetrahydrobiopterin<br>synthase/PTPS<br>6-pyruvoyl                                                 | Q03393 | 261640 | T67M       |
| tetrahydrobiopterin<br>synthase/PTPS<br>6-pyruvoyl                                                 | Q03393 | 261640 | VAL56MET   |
| Glutamate<br>decarboxylase 1 (brain,<br>67kD)                                                      | M81883 | 266100 | none found |
| Human hydroxyindole-<br>O-methyltransferase<br>promoter A-derived<br>(HIOMT) mRNA,<br>complete cds | U11090 | 300015 | none found |

|                                                        |               |        |                         |
|--------------------------------------------------------|---------------|--------|-------------------------|
| angiotensin II receptor<br>type 2/AGTR2                | U10273        | 300034 | none found              |
| P2Y4 pyrimidinergic<br>receptor/Gi protein-<br>coupled | NM_0025<br>65 | 300038 | none found              |
| Gamma-Aminobutyric<br>Acid Receptor,<br>Epsilon; Gabre | Y09765        | 300093 | none found              |
| bombesin-like receptor<br>3/BRS3                       | NM_0017<br>27 | 300107 | none found              |
| Glutamate<br>dehydrogenase 2                           | U08997        | 300144 | none found              |
| ACETYLCHOLINERGIC<br>N<br>METHYLTRANSFERASE-LIKE       | 300162        | 300162 | none found              |
| Arginine vasopressin<br>receptor 2                     | AF030626      | 304800 | 1-BP DEL                |
| Arginine vasopressin<br>receptor 2                     | AF030626      | 304800 | 1-BP DEL, 102G          |
| Arginine vasopressin<br>receptor 2                     | AF030626      | 304800 | 1-BP INS frameshift     |
| Arginine vasopressin<br>receptor 2                     | AF030626      | 304800 | 1-BP INS 804 frameshift |
| Arginine vasopressin<br>receptor 2                     | AF030626      | 304800 | 15delC                  |
| Arginine vasopressin<br>receptor 2                     | AF030626      | 304800 | 28-bp del               |
| Arginine vasopressin<br>receptor 2                     | AF030626      | 304800 | 786delG frameshift      |
| Arginine vasopressin                                   | AF030626      | 304800 | CpG dinucleotides       |



|                                 |           |  |  |  |
|---------------------------------|-----------|--|--|--|
| receptor 2                      | ALA132ASP |  |  |  |
| Arginine vasopressin receptor 2 | ARG181CYS |  |  |  |
| Arginine vasopressin receptor 2 | ARG113TRP |  |  |  |
| Arginine vasopressin receptor 2 | ARG203CYS |  |  |  |
| Arginine vasopressin receptor 2 | ARG337TER |  |  |  |
| Arginine vasopressin receptor 2 | ASP85ASN  |  |  |  |
| Arginine vasopressin receptor 2 | G107E     |  |  |  |
| Arginine vasopressin receptor 2 | GLY185CYS |  |  |  |
| Arginine vasopressin receptor 2 | GLY201ASP |  |  |  |
| Arginine vasopressin receptor 2 | L43P      |  |  |  |
| Arginine vasopressin receptor 2 | P322H     |  |  |  |
| Arginine vasopressin receptor 2 | P322S     |  |  |  |
| Arginine vasopressin receptor 2 | R137H     |  |  |  |
| Arginine vasopressin receptor 2 | TRP71TER  |  |  |  |
| Arginine vasopressin receptor 2 | TYR205CYS |  |  |  |

|                                                               |          |        |                                               |
|---------------------------------------------------------------|----------|--------|-----------------------------------------------|
| Arginine vasopressin receptor 2                               | AF030626 | 304800 | TYR280CYS                                     |
| Arginine vasopressin receptor 2                               | AF030626 | 304800 | W193X                                         |
| Gamma-Aminobutyric Acid Receptor, Alpha-3; Gabra3             | S62908   | 305660 | 16-repeat allele                              |
| Gamma-Aminobutyric Acid Receptor, Alpha-3; Gabra3             | S62908   | 305660 | Dinucleotide repeat                           |
| gastrin-releasing polypeptide receptor/G protein-coupled/GRPR | D87058   | 305670 | two single nucleotide substitutions in exon 2 |
| Glutamate Receptor, Ionotropic, Ampa 3; Glra3                 | X82068   | 305915 | none found                                    |
| Glycine Receptor, Alpha-2 Subunit; Glra2                      | X52008   | 305990 | none found                                    |
| Monoamine Oxidase A; MAOA                                     | M69226   | 309850 | 23-bp VNTR                                    |
| Monoamine Oxidase A; MAOA                                     | M69226   | 309850 | 3rd base of codon 941 941 G>T                 |
| Monoamine Oxidase A; MAOA                                     | M69226   | 309850 | A1026T ProlineProline                         |
| Monoamine Oxidase A; MAOA                                     | M69226   | 309850 | A1559G LysineArginine                         |
| Monoamine Oxidase A; MAOA                                     | M69226   | 309850 | A385C ArginineArginine <sub>e</sub>           |
| Monoamine Oxidase A; MAOA                                     | M69226   | 309850 | C1410T Aspartic AcidAspartic                  |

|                                       |        |        |                                                         |
|---------------------------------------|--------|--------|---------------------------------------------------------|
| Monoamine Oxidase<br>A; MAOA          | M69226 | 309850 | Acid<br>C886T Glutamine296T<br>ermination<br>codon      |
| Monoamine Oxidase<br>A; MAOA          | M69226 | 309850 | C886T GlutamineTermin<br>ation codon                    |
| Monoamine Oxidase<br>A; MAOA          | M69226 | 309850 | exon 14 -- RFLP<br>(EcoRV enzyme)                       |
| Monoamine Oxidase<br>A; MAOA          | M69226 | 309850 | length of (CA) <sub>n</sub><br>repeat                   |
| Monoamine Oxidase<br>A; MAOA          | M69226 | 309850 | RFLP (EcoRV<br>enzyme)                                  |
| Monoamine Oxidase<br>A; MAOA          | M69226 | 309850 | RFLP (Pst I)                                            |
| Monoamine Oxidase<br>A; MAOA          | M69226 | 309850 | T891G ArginineArginin<br>e                              |
| Monoamine Oxidase<br>A; MAOA          | M69226 | 309850 | T891G                                                   |
| Monoamine Oxidase<br>B; MAOB          | M69177 | 309860 | (GT) <sub>n</sub> repeat                                |
| Monoamine Oxidase<br>B; MAOB          | M69177 | 309860 | 36 bases upstream<br>from intron 13-exon<br>14 boundary |
| Monoamine Oxidase<br>B; MAOB          | M69177 | 309860 | A at position 644 of<br>intron 13                       |
| Monoamine Oxidase<br>B; MAOB          | M69177 | 309860 | G at position 644 of<br>intron 13                       |
| Monoamine Oxidase<br>B; MAOB          | M69177 | 309860 | RFLP (MaeIII<br>enzyme)                                 |
| serotonin 5-HT<br>receptors 5-HT1C, G | U49516 | 312861 | 2831T > G in the 3'                                     |

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|                                                          |        |        |                             |
|----------------------------------------------------------|--------|--------|-----------------------------|
| protein-coupled<br>serotonin 5-HT<br>receptors 5-HT1C, G | U49516 | 312861 | CYS23SER                    |
| protein-coupled                                          |        |        |                             |
| androgen receptor                                        | M20132 | 313700 | Hind III                    |
| androgen receptor                                        | M20132 | 313700 | (CAA)n                      |
| androgen receptor                                        | M20132 | 313700 | (CAG)n                      |
| androgen receptor                                        | M20132 | 313700 | (GGN)n                      |
| androgen receptor                                        | M20132 | 313700 | 5-KB DEL, EX F, G           |
| androgen receptor                                        | M20132 | 313700 | 5-KB DEL, EX E              |
| androgen receptor                                        | M20132 | 313700 | C>T within exon B silent    |
| androgen receptor                                        | M20132 | 313700 | CAG340TAG Gln>Ter           |
| androgen receptor                                        | M20132 | 313700 | Del T at 3286 frameshift    |
| androgen receptor                                        | M20132 | 313700 | dell893 frameshift          |
| androgen receptor                                        | M20132 | 313700 | G Codon 210 A               |
| androgen receptor                                        | M20132 | 313700 | G Codon 211 A               |
| androgen receptor                                        | M20132 | 313700 | G2314A ala>thr              |
| androgen receptor                                        | M20132 | 313700 | G2677A glu629arg            |
| androgen receptor                                        | M20132 | 313700 | HhaI                        |
| androgen receptor                                        | M20132 | 313700 | HpaII                       |
| androgen receptor                                        | M20132 | 313700 | Insert of 69<br>nucleotides |
| androgen receptor                                        | M20132 | 313700 | MaeIII                      |
| androgen receptor                                        | M20132 | 313700 | PARTIAL DEL                 |
| androgen receptor                                        | M20132 | 313700 | Stu I                       |
| androgen receptor                                        | M20132 | 313700 | 598 or 599 ter              |
| androgen receptor                                        | M20132 | 313700 | ALA721THR                   |
| androgen receptor                                        | M20132 | 313700 | ALA771THR                   |
| androgen receptor                                        | M20132 | 313700 | ARG607GLN                   |
| androgen receptor                                        | M20132 | 313700 | ARG608LYS                   |
| androgen receptor                                        | M20132 | 313700 | Arg615His                   |

|                   |        |        |           |
|-------------------|--------|--------|-----------|
| androgen receptor | M20132 | 313700 | arg726leu |
| androgen receptor | M20132 | 313700 | Arg752Gln |
| androgen receptor | M20132 | 313700 | ARG772CYS |
| androgen receptor | M20132 | 313700 | ARG773CYS |
| androgen receptor | M20132 | 313700 | ARG773HIS |
| androgen receptor | M20132 | 313700 | ARG839CYS |
| androgen receptor | M20132 | 313700 | ARG839HIS |
| androgen receptor | M20132 | 313700 | arg840his |
| androgen receptor | M20132 | 313700 | ARG846HIS |
| androgen receptor | M20132 | 313700 | ARG855HIS |
| androgen receptor | M20132 | 313700 | CYS579PHE |
| androgen receptor | M20132 | 313700 | G214R     |
| androgen receptor | M20132 | 313700 | GLN60TER  |
| androgen receptor | M20132 | 313700 | Gln798Glu |
| androgen receptor | M20132 | 313700 | GLN902ARG |
| androgen receptor | M20132 | 313700 | GLU2LYS   |
| androgen receptor | M20132 | 313700 | gly743val |
| androgen receptor | M20132 | 313700 | HIS874TYR |
| androgen receptor | M20132 | 313700 | ILE869MET |
| androgen receptor | M20132 | 313700 | LEU172TER |
| androgen receptor | M20132 | 313700 | LEU676PRO |
| androgen receptor | M20132 | 313700 | LEU707ARG |
| androgen receptor | M20132 | 313700 | LYS588TER |
| androgen receptor | M20132 | 313700 | LYS882TER |
| androgen receptor | M20132 | 313700 | MET780ILE |
| androgen receptor | M20132 | 313700 | MET786VAL |
| androgen receptor | M20132 | 313700 | PHE582TYR |
| androgen receptor | M20132 | 313700 | PRO546SER |
| androgen receptor | M20132 | 313700 | pro892ser |
| androgen receptor | M20132 | 313700 | SER647ASN |
| androgen receptor | M20132 | 313700 | THR877ALA |

|                         |         |        |                     |
|-------------------------|---------|--------|---------------------|
| androgen receptor       | M20132  | 313700 | THR877SER           |
| androgen receptor       | M20132  | 313700 | TRP717TER           |
| androgen receptor       | M20132  | 313700 | TRP794TER           |
| androgen receptor       | M20132  | 313700 | TYR761CYS           |
| androgen receptor       | M20132  | 313700 | val 581 phe         |
| androgen receptor       | M20132  | 313700 | VAL730MET           |
| androgen receptor       | M20132  | 313700 | VAL865LEU           |
| androgen receptor       | M20132  | 313700 | VAL865MET           |
| androgen receptor       | M20132  | 313700 | VAL866MET           |
| ACETYL-SEROTONI         |         | 402500 | none found          |
| N                       |         |        |                     |
| METHYLTRANSFER          |         |        |                     |
| ASE, Y-                 |         |        |                     |
| CHROMOSOMAL             |         |        |                     |
| voltage dependent       | U07139  | 600003 | none found          |
| calcium channel beta 2  |         |        |                     |
| subunit/ACNB2           |         |        |                     |
| vascular angiotensin II | NM_0048 | 600015 | none found          |
| receptor type           | 35      |        |                     |
| 1B/AGTR1B               |         |        |                     |
| Opioid Receptor, Mu-    | NM_0009 | 600018 | (CA)n               |
| 1; Oprm1                | 14      |        |                     |
| Opioid Receptor, Mu-    | NM_0009 | 600018 | Asn40Asp            |
| 1; Oprm1                | 14      |        |                     |
| P2Y2 purinoceptor/G     | U07225  | 600041 | none found          |
| protein-coupled         |         |        |                     |
| Solute Carrier Family   | U03504  | 600111 | none found          |
| 1, Member 3; Slc1a3     |         |        |                     |
| type V voltage          | NM_0003 | 600163 | 1-BP DEL frameshift |
| dependent sodium        | 35      |        |                     |
| channel alpha           |         |        |                     |

|                                                                      |               |        |                                                  |  |
|----------------------------------------------------------------------|---------------|--------|--------------------------------------------------|--|
| subunit:SCN5A<br>type V voltage<br>dependent sodium<br>channel alpha | NM_0003<br>35 | 600163 | 2-BP INS                                         |  |
| subunit:SCN5A<br>type V voltage<br>dependent sodium<br>channel alpha | NM_0003<br>35 | 600163 | LYS1505/PROI<br>506/GLN1507D<br>EL<br>ARG1232TRP |  |
| subunit:SCN5A<br>type V voltage<br>dependent sodium<br>channel alpha | NM_0003<br>35 | 600163 | ARG1623GLN                                       |  |
| subunit:SCN5A<br>type V voltage<br>dependent sodium<br>channel alpha | NM_0003<br>35 | 600163 | ARG1644HIS]                                      |  |
| subunit:SCN5A<br>type V voltage<br>dependent sodium<br>channel alpha | NM_0003<br>35 | 600163 | GLU1784LYS                                       |  |
| subunit:SCN5A<br>type V voltage<br>dependent sodium<br>channel alpha | NM_0003<br>35 | 600163 | THR1620MET                                       |  |
| subunit:SCN5A<br>Histamine receptor H1                               | AF026261      | 600167 | none found                                       |  |
| Gamma-Aminobutyric                                                   | S77553        | 600232 | none found                                       |  |

|                                                                     |               |        |                      |           |
|---------------------------------------------------------------------|---------------|--------|----------------------|-----------|
| Acid Receptor, Beta-2;<br>Gabbr2                                    | NM_0008<br>16 | 600233 | none found           |           |
| Gamma-Aminobutyric<br>Acid<br>Receptor; Gamma-3;<br>Gabbr3          | NM_0010<br>37 | 600235 |                      | CYS121TRP |
| type I voltage<br>dependent sodium<br>channel beta<br>subunit/SCN1B |               |        |                      |           |
| Arginine Vasopressin<br>Receptor 1B/AVPR1B                          | AF030512      | 600264 | none found           |           |
| Glutamate Receptor,<br>Ionotropic, Kainate 4;<br>Grik4              | S67803        | 600282 | none found           |           |
| Glutamate Receptor,<br>Ionotropic, Kainate 5;<br>Grik5              | S40369        | 600283 | none found           |           |
| Solute Carrier Family<br>1, Member 2; Slc1a2                        | U03505        | 600300 | none found           |           |
| Vesicular acetylcholine<br>transporter                              | NM_0030<br>55 | 600336 | none found           |           |
| bradykinin receptor<br>B1/BDKRB1 G<br>protein-coupled               | NM_0007<br>10 | 600337 | 9-base pair deletion |           |
| bradykinin receptor<br>B1/BDKRB1 G<br>protein-coupled               | NM_0007<br>10 | 600337 | A1098-->G            |           |
| bradykinin receptor<br>B1/BDKRB1 G<br>protein-coupled               | NM_0007<br>10 | 600337 | C181-->T             |           |

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|                                                                             |               |        |            |
|-----------------------------------------------------------------------------|---------------|--------|------------|
| bradykinin receptor<br>B1/BDKRB1 G<br>protein-coupled                       | NM_0007<br>10 | 600337 | G-699-->C  |
| Glycine Receptor,<br>Alpha-3 Subunit; Glra3                                 | AF018157      | 600421 | none found |
| Adenosine A3<br>Receptor; Adora3/G<br>protein-coupled                       | L20463        | 600445 | none found |
| Adenosine A2b<br>Receptor; Adora2b/G<br>protein-coupled                     | X68487        | 600446 | none found |
| neurotrophic tyrosine<br>kinase receptor type<br>2/NTRK2                    | NM_0061<br>80 | 600456 | none found |
| inwardly rectifying<br>potassium channel,<br>subfamily J, member<br>4/KCNJ4 | NM_0049<br>81 | 600504 | none found |
| reelin/RELN                                                                 | NM_0050<br>45 | 600514 | none found |
| Human immunophilin<br>(FKBP52) mRNA,<br>complete cds                        | M88279        | 600611 | none found |
| opioid binding cell<br>adhesion<br>molecule OBCAM                           | *****         | 600632 | none found |
| Solute carrier family 1,<br>member 6<br>(GABA/GLU)/SLC1A<br>6               | NM_0050<br>71 | 600637 | none found |
| Human aryl                                                                  | L19956        | 600641 | none found |

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|                                                                 |               |        |            |
|-----------------------------------------------------------------|---------------|--------|------------|
| leptin receptor/LEPR                                            | 03<br>NM_0023 | 601007 | K109R      |
| leptin receptor/LEPR                                            | 03<br>NM_0023 | 601007 | K656N      |
| leptin receptor/LEPR                                            | 03<br>NM_0023 | 601007 | Lys109Arg  |
| leptin receptor/LEPR                                            | 03<br>NM_0023 | 601007 | Lys656Asn  |
| leptin receptor/LEPR                                            | 03<br>NM_0023 | 601007 | Pro1019Pro |
| leptin receptor/LEPR                                            | 03<br>NM_0023 | 601007 | Ser343Ser  |
| leptin receptor/LEPR                                            | 03<br>NM_0023 | 601007 | Ser492Thr  |
| Solute carrier family 6,<br>Member 9; SLC6A9<br>(glycine)       | S70612        | 601019 | none found |
| serotonin 5-HT<br>receptors 5-HT6, G<br>protein-coupled         | L41147        | 601109 | C267T      |
| Glutamate Receptor,<br>Metabotropic 3/G<br>protein-coupled/Grm3 | X77748        | 601115 | none found |
| Glutamate Receptor,<br>Metabotropic 8/G<br>protein-coupled/Grm8 | U95025        | 601116 | none found |
| Thimet oligopeptidase                                           | Z50115        | 601117 | none found |
| serotonin 5-HT<br>receptors 5-HT2B, G<br>protein-coupled        | X77307        | 601122 | none found |

|                                                                                                                                                   |           |        |            |
|---------------------------------------------------------------------------------------------------------------------------------------------------|-----------|--------|------------|
| P2Y <sub>1</sub> purinoceptor/G protein-coupled type II voltage dependent sodium channel alpha 2 subunit/SCN2A2                                   | U42029    | 601167 | none found |
| 11 sapiens mRNA for aryl sulfotransferase (ST1A2)                                                                                                 | M55662    | 601219 | none found |
| serotonin 5-HT receptor 5-HT5a, G protein-coupled type II voltage dependent sodium channel beta subunit/SCN2B                                     | X78282    | 601292 | none found |
| 11 sapiens mRNA for prepronociceptin                                                                                                              | X81411    | 601305 | none found |
| P2Y <sub>7</sub> purinoceptor/leukotriene B4 receptor/G protein-coupled G protein coupled potassium channel, subfamily J, member 3/KCNJ6/GIRK1    | NM_004588 | 601327 | none found |
| 11 sapiens mRNA for purinoceptor/leukotriene B4 receptor/G protein-coupled G protein coupled potassium channel, subfamily J, member 3/KCNJ6/GIRK1 | X97370    | 601459 | none found |
| estrogen receptor 2 (ESR2)                                                                                                                        | NM_000752 | 601531 | none found |
| voltage dependent potassium channel, subfamily K, member                                                                                          | NM_002239 | 601534 | (CA)n      |
|                                                                                                                                                   | X99101    | 601663 | none found |
|                                                                                                                                                   | NM_002245 | 601745 | none found |

|              |         |        |         |                                 |
|--------------|---------|--------|---------|---------------------------------|
| 1/KUNLI      | NM_0003 | 601769 | A(T/C)G | putative translation start site |
| vitamin D    | 76      |        |         |                                 |
| rec.ptor VDR |         |        |         |                                 |
| vitamin D    | NM_0003 | 601769 | Apal    |                                 |
| rec.ptor VDR | 76      |        |         |                                 |
| vitamin D    | NM_0003 | 601769 | BsmI    |                                 |
| rec.ptor VDR | 76      |        |         |                                 |
| vitamin D    | NM_0003 | 601769 | FokI    |                                 |
| rec.ptor VDR | 76      |        |         |                                 |
| vitamin D    | NM_0003 | 601769 | PvuII   |                                 |
| rec.ptor VDR | 76      |        |         |                                 |
| vitamin D    | NM_0003 | 601769 | TaqI    |                                 |
| rec.ptor VDR | 76      |        |         |                                 |
| vitamin D    | NM_0003 | 601769 | XbaI    |                                 |
| rec.ptor VDR | 76      |        |         |                                 |
| vitamin D    | NM_0003 | 601769 |         | ARG-GLY                         |
| rec.ptor VDR | 76      |        |         |                                 |
| vitamin D    | NM_0003 | 601769 |         | ARG391CYS                       |
| rec.ptor VDR | 76      |        |         |                                 |
| vitamin D    | NM_0003 | 601769 |         | HIS305GLN                       |
| rec.ptor VDR | 76      |        |         |                                 |
| vitamin D    | NM_0003 | 601769 |         | ILE314SER                       |
| rec.ptor VDR | 76      |        |         |                                 |
| vitamin D    | NM_0003 | 601769 |         | ARG271LEU                       |
| rec.ptor VDR | 76      |        |         |                                 |
| vitamin D    | NM_0003 | 601769 |         | ARG30TER                        |
| rec.ptor VDR | 76      |        |         |                                 |
| vitamin D    | NM_0003 | 601769 |         | ARG47GLN                        |
| rec.ptor VDR | 76      |        |         |                                 |
| vitamin D    | NM_0003 | 601769 |         | ARG77GLN                        |
| rec.ptor VDR | 76      |        |         |                                 |

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|                        |           |        |                        |
|------------------------|-----------|--------|------------------------|
| receptor VDR           | 76        | 601769 | codon 352              |
| vitamin D              | NM_000376 |        |                        |
| receptor VDR           | 76        | 601769 | GLN149TER              |
| vitamin D              | NM_000376 |        |                        |
| receptor VDR           | 76        | 601769 | GLY30ASP               |
| vitamin D              | NM_000376 |        |                        |
| receptor VDR           | 76        | 601769 | GLY46ASP               |
| vitamin D              | NM_000376 |        |                        |
| receptor VDR           | 76        | 601769 | TYR292TER              |
| vitamin D              | NM_000376 |        |                        |
| receptor VDR           | 76        | 601770 | none found             |
| Neuropptide Y          | D86519    |        |                        |
| receptor Y6            | 76        | 601784 | none found             |
| voltage independent    | NM_001094 |        |                        |
| neuronal sodium        | 94        |        |                        |
| channel 1/ACCN1        |           | 601949 | none found             |
| voltage dependent      | *****     |        |                        |
| calcium channel beta 4 |           | 601958 | none found             |
| subunit 4/ACNB4        |           |        |                        |
| voltage dependent      |           | 601970 | none found             |
| calcium channel beta 3 | NM_000725 |        |                        |
| subunit 3/ACNB3        |           |        |                        |
| vasoactive intestinal  | L40764    |        |                        |
| peptide receptor       |           |        |                        |
| 2A/OPR                 |           |        |                        |
| RAA related orphan     | *****     | 601972 | none found             |
| receptor 13/RORB       |           |        |                        |
| Opioid Receptor,       | U75283    | 601978 | Gln2Pro                |
| Signaling              |           |        |                        |
| Opioid Receptor,       | U75283    | 601978 | GC-241-240TT in the 5' |
| Signaling              |           |        |                        |

|                                                                          |           |        |                            |
|--------------------------------------------------------------------------|-----------|--------|----------------------------|
| Neuropeptide Y receptor Y5                                               | U94320    | 602001 | none found                 |
| Catecholaminergic receptor 2                                             | NM_001883 | 602034 | none found                 |
| neuropilin 1/VEGF receptor                                               | NM_003873 | 602069 | none found                 |
| neuropilin 2/VEGF receptor NP2                                           | NM_003872 | 602070 | none found                 |
| Solute carrier family 29 (nucleosides), member 2/SCL29A2/ENT2            | X86681    | 602110 | none found                 |
| serotonin 5-HT receptor 5-HT4, G protein-coupled                         | Y08756    | 602164 | none found                 |
| Solute carrier family 29 (nucleosides), member 1/SCL29A1/ENT1            | NM_004955 | 602193 | none found                 |
| inwardly-rectifying potassium channel, subfamily J, member 10/KCNJ10     | *****     | 602208 | none found                 |
| voltage-dependent potassium channel, KCa1-like subfamily, member 3/KCNQ3 | AF033347  | 602232 | GLY263VAL                  |
| voltage-dependent potassium channel, KCa1-like subfamily, member 2/KCNQ2 | NM_000218 | 602235 | 1-BP DEL, 1846T frameshift |
| voltage-dependent potassium channel, KCa1-like subfamily, member 2/KCNQ2 | NM_000218 | 602235 | 5-BP INS frameshift        |

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|                                                                              |           |        |            |
|------------------------------------------------------------------------------|-----------|--------|------------|
| D-Asp 2d; Grin2d                                                             |           |        |            |
| Gamma-Aminobutyric Acid Receptor, Pi;                                        | U95367    | 602729 | none found |
| Galap                                                                        |           |        |            |
| cyclic nucleotide gated hyperpolarization activated potassium channel 1/HCN1 | AF064876  | 602780 | none found |
| cyclic nucleotide gated hyperpolarization activated potassium channel 2/HCN2 | AF064877  | 602781 | none found |
| Purinergic Receptor P2X; Ligand-Gated Ion Channel 5; P2rx5                   | NM_002561 | 602836 | none found |
| voltage independent neuronal sodium channel 2/ACCN2                          | NM_001095 | 602866 | none found |
| voltage dependent potassium channel, subfamily S, member 1/KCNK1             | *****     | 602905 | none found |
| voltage dependent potassium channel, subfamily S, member 2/KCNK2             | *****     | 602906 | none found |
| neuronal voltage dependent calcium channel gamma subunit CACNG2              | *****     | 602911 | none found |
| RA related orphan                                                            | NM_0050   | 602943 | none found |

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SD. 14.1.1

|                                      |           |        |                                         |
|--------------------------------------|-----------|--------|-----------------------------------------|
| thyroid stimulating hormone receptor | NM_000369 | 603372 | 2 bases deleted of codon 655            |
| thyroid stimulating hormone receptor | NM_000369 | 603372 | C253A                                   |
| thyroid stimulating hormone receptor | NM_000369 | 603372 | duplication of nucleotides -346 to -330 |
| thyroid stimulating hormone receptor | NM_000369 | 603372 | G to C +3 intron 6                      |
| thyroid stimulating hormone receptor | NM_000369 | 603372 | G-A -4 intron                           |
| thyroid stimulating hormone receptor | NM_000369 | 603372 | TaqI                                    |
| thyroid stimulating hormone receptor | NM_000369 | 603372 | CYS41SER                                |
| thyroid stimulating hormone receptor | NM_000369 | 603372 | LEU629PHE                               |
| thyroid stimulating hormone receptor | NM_000369 | 603372 | SER505ASN                               |
| thyroid stimulating hormone receptor | NM_000369 | 603372 | ALA553THR                               |
| thyroid stimulating hormone receptor | NM_000369 | 603372 | ALA623ILE                               |
| thyroid stimulating hormone receptor | NM_000369 | 603372 | alanine 623 to valine                   |
| thyroid stimulating hormone receptor | NM_000369 | 603372 | ARG109GLN                               |
| thyroid stimulating hormone receptor | NM_000369 | 603372 | Asn715Asp                               |
| thyroid stimulating hormone receptor | NM_000369 | 603372 | Asp219Glu                               |

|                                         |               |        |              |
|-----------------------------------------|---------------|--------|--------------|
| thyroid stimulating<br>hormone receptor | NM_0003<br>69 | 603372 | ASP36HIS     |
| thyroid stimulating<br>hormone receptor | NM_0003<br>69 | 603372 | ASP410ASN    |
| thyroid stimulating<br>hormone receptor | NM_0003<br>69 | 603372 | ASP619GLY    |
| thyroid stimulating<br>hormone receptor | NM_0003<br>69 | 603372 | ASP633HIS    |
| thyroid stimulating<br>hormone receptor | NM_0003<br>69 | 603372 | asp727glu    |
| thyroid stimulating<br>hormone receptor | NM_0003<br>69 | 603372 | Asp727Glu    |
| thyroid stimulating<br>hormone receptor | NM_0003<br>69 | 603372 | CAG          |
| thyroid stimulating<br>hormone receptor | NM_0003<br>69 | 603372 | [Glu]227CAT  |
| thyroid stimulating<br>hormone receptor | NM_0003<br>69 | 603372 | [His]        |
| thyroid stimulating<br>hormone receptor | NM_0003<br>69 | 603372 | CYS390TRP    |
| thyroid stimulating<br>hormone receptor | NM_0003<br>69 | 603372 | CYS672TYR    |
| thyroid stimulating<br>hormone receptor | NM_0003<br>69 | 603372 | GCG          |
| thyroid stimulating<br>hormone receptor | NM_0003<br>69 | 603372 | [Ala]460GCA  |
| thyroid stimulating<br>hormone receptor | NM_0003<br>69 | 603372 | [Ala]        |
| thyroid stimulating<br>hormone receptor | NM_0003<br>69 | 603372 | GGT[Arg]201C |
| thyroid stimulating<br>hormone receptor | NM_0003<br>69 | 603372 | AT [His]     |
| thyroid stimulating<br>hormone receptor | NM_0003<br>69 | 603372 | GLN324TER    |
| thyroid stimulating<br>hormone receptor | NM_0003<br>69 | 603372 | ILE167ASN    |
| thyroid stimulating<br>hormone receptor | NM_0003<br>69 | 603372 | leu677val    |
| thyroid stimulating<br>hormone receptor | NM_0003<br>69 | 603372 | LYS183ARG    |

SD...H1111

|                       |          |        |  |            |
|-----------------------|----------|--------|--|------------|
| hormone receptor      | 69       |        |  | Lys723 Met |
| thyroid stimulating   | NM_0003  | 603372 |  |            |
| hormone receptor      | 69       |        |  |            |
| thyroid stimulating   | NM_0003  | 603372 |  | MET453THR  |
| hormone receptor      | 69       |        |  |            |
| thyroid stimulating   | NM_0003  | 603372 |  | P52T       |
| hormone receptor      | 69       |        |  |            |
| thyroid stimulating   | NM_0003  | 603372 |  | Phe197Ile  |
| hormone receptor      | 69       |        |  |            |
| thyroid stimulating   | NM_0003  | 603372 |  | PHE525LEU  |
| hormone receptor      | 69       |        |  |            |
| thyroid stimulating   | NM_0003  | 603372 |  | PHE631LEU  |
| hormone receptor      | 69       |        |  |            |
| thyroid stimulating   | NM_0003  | 603372 |  | PRO162ALA  |
| hormone receptor      | 69       |        |  |            |
| thyroid stimulating   | NM_0003  | 603372 |  | SER281ASN  |
| hormone receptor      | 69       |        |  |            |
| thyroid stimulating   | NM_0003  | 603372 |  | SER281ILE  |
| hormone receptor      | 69       |        |  |            |
| thyroid stimulating   | NM_0003  | 603372 |  | TRP546TER  |
| hormone receptor      | 69       |        |  |            |
| thyroid stimulating   | NM_0003  | 603372 |  | VAL509ALA  |
| hormone receptor      | 69       |        |  |            |
| type IX voltage       | NM_0029  | 603415 |  | none found |
| dependent sodium      | 77       |        |  |            |
| channel alpha         |          |        |  |            |
| subunit SCN9A         |          |        |  |            |
| homolog of Drosophila | AF071062 | 603448 |  | none found |
| dishevelled DAB1      |          |        |  |            |
| Gamma-Aminobutyric    | Y11044   | 603540 |  | none found |
| Ac 1B Receptor 1;     |          |        |  |            |

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|                                                                               |               |        |            |
|-------------------------------------------------------------------------------|---------------|--------|------------|
| Ga-bri                                                                        | *****         | 603659 | none found |
| glutagon-like peptide 2<br>receptor:GLP2R                                     |               |        |            |
| Amine oxidase<br>(copper-containing)                                          | AF054985      | 603735 | none found |
| 3/A OC3                                                                       |               |        |            |
| voltage dependent<br>potassium channel,<br>subfamily F, member<br>1/KCNF1     | NM_0022<br>36 | 603787 | none found |
| voltage dependent<br>potassium channel,<br>subfamily S, member<br>3/B CNK3    | AF043472      | 603888 | none found |
| inwardly rectifying<br>potassium channel,<br>subfamily J, member<br>14/KCNJ14 | *****         | 603953 | none found |
| sodium channel alpha-<br>subunit SCN4A                                        | U24693        | 603967 | (GA)n      |
| sodium channel alpha-<br>subunit SCN4A                                        | U24693        | 603967 | (GT)n      |
| sodium channel alpha-<br>subunit SCN4A                                        | U24693        | 603967 | GLY1306ALA |
| sodium channel alpha-<br>subunit SCN4A                                        | U24693        | 603967 | ALA1156THR |
| sodium channel alpha-<br>subunit SCN4A                                        | U24693        | 603967 | ARG1448CYS |
| sodium channel alpha-<br>subunit SCN4A                                        | U24693        | 603967 | ARG1448HIS |
| sodium channel alpha-<br>subunit SCN4A                                        | U24693        | 603967 | GLY1306VAL |

|                                      |        |        |            |
|--------------------------------------|--------|--------|------------|
| subunit/SCN4A                        | U24693 | 603967 | ILE1160VAL |
| sodium channel alpha-subunit/SCN4A   |        |        |            |
| sodium channel alpha-subunit/SCN4A   | U24693 | 603967 | LEU1433ARG |
| sodium channel alpha-subunit/SCN4A   |        |        |            |
| sodium channel alpha-subunit/SCN4A   | U24693 | 603967 | MET1592VAL |
| sodium channel alpha-subunit/SCN4A   |        |        |            |
| sodium channel alpha-subunit/SCN4A   | U24693 | 603967 | SER804PHE  |
| sodium channel alpha-subunit/SCN4A   |        |        |            |
| sodium channel alpha-subunit/SCN4A   | U24693 | 603967 | THR1313MET |
| sodium channel alpha-subunit/SCN4A   |        |        |            |
| sodium channel alpha-subunit/SCN4A   | U24693 | 603967 | THR704MET  |
| sodium channel alpha-subunit/SCN4A   |        |        |            |
| sodium channel alpha-subunit/SCN4A   | U24693 | 603967 | VAL1293ILE |
| sodium channel alpha-subunit/SCN4A   |        |        |            |
| sodium channel alpha-subunit/SCN4A   | U24693 | 603967 | VAL1589MET |
| sodium channel alpha-subunit/SCN4A   |        |        |            |
| sodium channel alpha-subunit/SCN4A   | U24693 | 603967 | VAL445MET  |
| sodium channel alpha-subunit/SCN4A   |        |        |            |
| Glutamate Receptor, Metabotropic 6/G | U82083 | 604096 | none found |
| protein-coupled/Grm6                 |        |        |            |
| Glutamate Receptor, Metabotropic 2/G | L35318 | 604099 | none found |
| protein-coupled/ Grm2                |        |        |            |
| Glutamate Receptor, Metabotropic 4/G | X80818 | 604100 | none found |
| protein-coupled/Grm4                 |        |        |            |
| Glutamate Receptor, Metabotropic 7/G | X94552 | 604101 | none found |
| protein-coupled/Grm7                 |        |        |            |



|                                                                                     |        |        |                            |
|-------------------------------------------------------------------------------------|--------|--------|----------------------------|
| Glutamate Receptor,<br>Metabotropic 5/G<br>protein-coupled/Grm5                     | D28538 | 604102 | none found                 |
| dihydrofolate reductase                                                             | J00140 | 126060 | 2 RFLP's                   |
| dihydrofolate reductase                                                             | J00140 | 126060 | intronic                   |
| FKBP, tacrolimus<br>binding protein,<br>FK506-binding protein<br>1 (12kD)           | M34539 | 186945 | polymorphism<br>none found |
| Cyclooxygenase 1<br>COX1                                                            | M59979 | 176805 | none found                 |
| Cyclooxygenase 2<br>COX2                                                            | M90100 | 600262 | none found                 |
| beta-synuclein [human,<br>brain, mRNA, 730 nt]<br>histamine N-<br>methyltransferase | S69965 | 602569 | none found                 |
| histamine N-<br>methyltransferase                                                   |        |        | A939G                      |
|                                                                                     |        |        | Thr105Ile                  |

Table 20. Identified  
Variances in Genes or  
Related Pathways  
involved in the  
Pharmacokinetics and  
Pharmacodynamics of  
Candidate Therapeutic  
Interventions

|                         |        |          |            |
|-------------------------|--------|----------|------------|
| 3'(2'), 5'-bisphosphate | 604053 | NM_00608 | none found |
|-------------------------|--------|----------|------------|

|                        |        |        |                     |
|------------------------|--------|--------|---------------------|
| nucleotidase 1/BPNT    | 5      |        |                     |
| Acetylcholinesterase/A | 100740 | M55040 | 1431 C/T 446 silent |
| CHE                    |        |        |                     |
| Acetylcholinesterase/A | 100740 | M55040 | 408 G/C arg561pro   |
| CHE                    |        |        |                     |
| Acetylcholinesterase/A | 100740 | M55040 | HIS322ASN           |
| CHE                    |        |        |                     |
| acyl-Coenzyme A        |        |        | none found          |
| dehydrogenase, C-4 to  |        |        |                     |
| C-12 straight          |        |        |                     |
| chain/ACADM            |        |        |                     |
| (mitochondrial)        |        |        |                     |
| ALCOHOL                | 103700 |        | none found          |
| DEHYDROGENASE          |        |        |                     |
| 1                      |        |        |                     |
| aldehyde               | 100650 | K03001 | GLU487LYS           |
| dehydrogenase          |        |        |                     |
| 2/ALDH2 (liver         |        |        |                     |
| mitochondria)          |        |        |                     |
| aldehyde               | 100650 | K03001 | A-361G              |
| dehydrogenase          |        |        |                     |
| 2/ALDH2 (liver         |        |        |                     |
| mitochondria)          |        |        |                     |
| aldehyde               | 100650 | K03001 | -357 G/A            |
| dehydrogenase          |        |        |                     |
| 2/ALDH2 (liver         |        |        |                     |
| mitochondria)          |        |        |                     |
| ALDEHYDE               | 100670 |        | C183T silent        |
| DEHYDROGENASE          |        |        |                     |
| 5                      |        |        |                     |
| ALDEHYDE               | 100670 |        | C257T Val<-->Ala    |

|                       |        |          |                  |  |           |
|-----------------------|--------|----------|------------------|--|-----------|
| DEHYDROGENASE         |        |          |                  |  |           |
| 5                     |        |          |                  |  |           |
| ALDEHYDE              | 100670 |          | T320G Arg<-->Leu |  |           |
| DEHYDROGENASE         |        |          |                  |  |           |
| 5                     |        |          |                  |  |           |
| ALDO-KETO             | 600449 |          | none found       |  |           |
| REDUCTASE             |        |          |                  |  |           |
| FAMILY 1, MEMBER      |        |          |                  |  |           |
| 1; AKR1C1             |        |          |                  |  |           |
| ALDO-KETO             | 103830 |          | none found       |  |           |
| REDUCTASE             |        |          |                  |  |           |
| FAMILY 1, MEMBER      |        |          |                  |  |           |
| A1; AKR1A1            |        |          |                  |  |           |
| ALDO-KETO             | 603966 |          | none found       |  |           |
| REDUCTASE             |        |          |                  |  |           |
| FAMILY 1, MEMBER      |        |          |                  |  |           |
| C3                    |        |          |                  |  |           |
| Aldo-keto reductase   | 600451 | *****    | none found       |  |           |
| family 1, member      |        |          |                  |  |           |
| C4/chlorodecone       |        |          |                  |  |           |
| reductase/AKR1C4      |        |          |                  |  |           |
| Aldo-keto reductase   | 603418 | NM_00368 | none found       |  |           |
| family 7; member      |        | 9        |                  |  |           |
| A2/aflatoxin aldehyde |        |          |                  |  |           |
| reductase/AKR7A2      |        |          |                  |  |           |
| anthracylcline        | 603234 | NM_00117 | none found       |  |           |
| resistance-related    |        | 1        |                  |  |           |
| protein/ARA           |        |          |                  |  |           |
| antigen peptide       | 170260 | NM_00059 |                  |  | ILE333VAL |
| transporter 1/MHC     |        | 3        |                  |  |           |
| 1/TAP1                |        |          |                  |  |           |

|                                          |        |           |                                  |
|------------------------------------------|--------|-----------|----------------------------------|
| antigen peptide transporter 1/MHC 1/TAP1 | 170260 | NM_000593 | ASP637GLY                        |
| antigen peptide transporter 1/MHC 1/TAP1 | 170260 | NM_000593 | ARG659GLN                        |
| antigen peptide transporter 1/MHC 1/TAP1 | 170260 | NM_000593 | val- leucine                     |
| antigen peptide transporter 1/MHC 1/TAP1 | 170260 | NM_000593 | silent glycine                   |
| antigen peptide transporter 1/MHC 1/TAP1 | 170260 | NM_000593 | silent glutamic acid             |
| antigen peptide transporter 1/MHC 1/TAP1 | 170260 | NM_000593 | silent alanine                   |
| antigen peptide transporter 1/MHC 1/TAP1 | 170260 | NM_000593 | GTC-->ATC Val518Ile              |
| antigen peptide transporter 1/MHC 1/TAP1 | 170260 | NM_000593 | G-->T promoter                   |
| antigen peptide transporter 1/MHC 1/TAP1 | 170260 | NM_000593 | 10-bp insert intron 9            |
| antigen peptide transporter 1/MHC 1/TAP1 | 170260 | NM_000593 | G-->T 80-bp 3' termination codon |
| antigen peptide transporter 1/MHC 1/TAP1 | 170260 | NM_000593 | dinucleotide repeat              |

|                                                |                      |                       |               |
|------------------------------------------------|----------------------|-----------------------|---------------|
| transporter 1/MHC<br>1/TAP1                    | 3                    | intron 3              |               |
| antigen peptide<br>transporter 2/MHC<br>2/TAP2 | 170261 NM_00054<br>4 |                       | ILE379VAL     |
| antigen peptide<br>transporter 2/MHC<br>2/TAP2 | 170261 NM_00054<br>4 |                       | ALA665THR     |
| antigen peptide<br>transporter 2/MHC<br>2/TAP2 | 170261 NM_00054<br>4 |                       | GLN687TER     |
| antigen peptide<br>transporter 2/MHC<br>2/TAP2 | 170261 NM_00054<br>4 |                       | Thr374Ala     |
| antigen peptide<br>transporter 2/MHC<br>2/TAP2 | 170261 NM_00054<br>4 | ACG to ACA 458Thr     |               |
| antigen peptide<br>transporter 2/MHC<br>2/TAP2 | 170261 NM_00054<br>4 | GGG to GGA 466Gly     |               |
| antigen peptide<br>transporter 2/MHC<br>2/TAP2 | 170261 NM_00054<br>4 | GTT to ATT 467Val-Ile |               |
| antigen peptide<br>transporter 2/MHC<br>2/TAP2 | 170261 NM_00054<br>4 | ATG-->GTG Met577Val   |               |
| antigen peptide<br>transporter 2/MHC<br>2/TAP2 | 170261 NM_00054<br>4 |                       | 565 (Ala-Thr) |
| antigen peptide<br>transporter 2/MHC           | 170261 NM_00054<br>4 | silent codon 386      |               |

## 2/TAP2

|                                                                     |        |               |                                                           |
|---------------------------------------------------------------------|--------|---------------|-----------------------------------------------------------|
| Aromatic L-Amino<br>Acid                                            | 107930 | M76180        | SspI                                                      |
| Decarboxylase/AADC/<br>dopa decarboxylase                           |        |               |                                                           |
| Aryl hydrocarbon<br>receptor nuclear<br>translocator-<br>like/ARNTL | 602550 | NM_00117<br>8 | none found                                                |
| Aryl hydrocarbon<br>receptor nuclear<br>translocator/ARNT           | 126110 | NM_00166<br>8 | MspI                                                      |
| Aryl hydrocarbon<br>receptor/AHR                                    | 600253 | NM_00162<br>1 | none found                                                |
| Arylsulfatase A/steroid<br>sulfatase/ARSA                           | 250100 | NM_00048<br>7 | A-to-G transition<br>changed the first<br>polyadenylation |
| Arylsulfatase A/steroid<br>sulfatase/ARSA                           | 250100 | NM_00048<br>7 | ARG350SER                                                 |
| Arylsulfatase A/steroid<br>sulfatase/ARSA                           | 250100 | NM_00048<br>7 | IVS2DS, G-A, +1                                           |
| Arylsulfatase A/steroid<br>sulfatase/ARSA                           | 250100 | NM_00048<br>7 | PRO426LEU                                                 |
| Arylsulfatase A/steroid<br>sulfatase/ARSA                           | 250100 | NM_00048<br>7 | GLY99ASP                                                  |
| Arylsulfatase A/steroid<br>sulfatase/ARSA                           | 250100 | NM_00048<br>7 | SER96PH                                                   |
| Arylsulfatase A/steroid<br>sulfatase/ARSA                           | 250100 | NM_00048<br>7 | 11-BP DEL, EX8                                            |
| Arylsulfatase A/steroid<br>sulfatase/ARSA                           | 250100 | NM_00048<br>7 | ILE-TO-SER,<br>EX3                                        |

|                                           |        |               |                  |           |
|-------------------------------------------|--------|---------------|------------------|-----------|
| Arylsulfatase A/steroid<br>sulfatase/ARSA | 250100 | NM_00048<br>7 | IVS7DS, G-A, +1  |           |
| Arylsulfatase A/steroid<br>sulfatase/ARSA | 250100 | NM_00048<br>7 |                  | ARG84GLN  |
| Arylsulfatase A/steroid<br>sulfatase/ARSA | 250100 | NM_00048<br>7 |                  | GLY309SER |
| Arylsulfatase A/steroid<br>sulfatase/ARSA | 250100 | NM_00048<br>7 | -BP DEL FS105TER |           |
| Arylsulfatase A/steroid<br>sulfatase/ARSA | 250100 | NM_00048<br>7 |                  | GLY86ASP  |
| Arylsulfatase A/steroid<br>sulfatase/ARSA | 250100 | NM_00048<br>7 |                  | SER96LEU  |
| Arylsulfatase A/steroid<br>sulfatase/ARSA | 250100 | NM_00048<br>7 |                  | GLY122SER |
| Arylsulfatase A/steroid<br>sulfatase/ARSA | 250100 | NM_00048<br>7 |                  | PRO136LEU |
| Arylsulfatase A/steroid<br>sulfatase/ARSA | 250100 | NM_00048<br>7 | 1-BP DEL, 297C   |           |
| Arylsulfatase A/steroid<br>sulfatase/ARSA | 250100 | NM_00048<br>7 |                  | GLY154ASP |
| Arylsulfatase A/steroid<br>sulfatase/ARSA | 250100 | NM_00048<br>7 |                  | PRO155ARG |
| Arylsulfatase A/steroid<br>sulfatase/ARSA | 250100 | NM_00048<br>7 |                  | PRO167ARG |
| Arylsulfatase A/steroid<br>sulfatase/ARSA | 250100 | NM_00048<br>7 |                  | ASP169ASN |
| Arylsulfatase A/steroid<br>sulfatase/ARSA | 250100 | NM_00048<br>7 |                  | ALA212VAL |
| Arylsulfatase A/steroid<br>sulfatase/ARSA | 250100 | NM_00048<br>7 |                  | ALA224VAL |
| Arylsulfatase A/steroid<br>sulfatase/ARSA | 250100 | NM_00048<br>7 |                  | PRO231THR |

|                         |        |          |                 |           |
|-------------------------|--------|----------|-----------------|-----------|
| sulfatase/ARSA          | 7      |          |                 |           |
| Arylsulfatase A/steroid | 250100 | NM_00048 |                 | ARG244CYS |
| sulfatase/ARSA          | 7      |          |                 |           |
| Arylsulfatase A/steroid | 250100 | NM_00048 |                 | GLY245ARG |
| sulfatase/ARSA          | 7      |          |                 |           |
| Arylsulfatase A/steroid | 250100 | NM_00048 |                 | THR274MET |
| sulfatase/ARSA          | 7      |          |                 |           |
| Arylsulfatase A/steroid | 250100 | NM_00048 | IVS4DS, G-A, +1 |           |
| sulfatase/ARSA          | 7      |          |                 |           |
| Arylsulfatase A/steroid | 250100 | NM_00048 |                 | ARG288CYS |
| sulfatase/ARSA          | 7      |          |                 |           |
| Arylsulfatase A/steroid | 250100 | NM_00048 |                 | SER295TYR |
| sulfatase/ARSA          | 7      |          |                 |           |
| Arylsulfatase A/steroid | 250100 | NM_00048 |                 | GLY325CYS |
| sulfatase/ARSA          | 7      |          |                 |           |
| Arylsulfatase A/steroid | 250100 | NM_00048 |                 | ASP335VAL |
| sulfatase/ARSA          | 7      |          |                 |           |
| Arylsulfatase A/steroid | 250100 | NM_00048 |                 | ARG370TRP |
| sulfatase/ARSA          | 7      |          |                 |           |
| Arylsulfatase A/steroid | 250100 | NM_00048 |                 | ARG370GLN |
| sulfatase/ARSA          | 7      |          |                 |           |
| Arylsulfatase A/steroid | 250100 | NM_00048 |                 | PRO377LEU |
| sulfatase/ARSA          | 7      |          |                 |           |
| Arylsulfatase A/steroid | 250100 | NM_00048 |                 | GLU382LYS |
| sulfatase/ARSA          | 7      |          |                 |           |
| Arylsulfatase A/steroid | 250100 | NM_00048 |                 | ARG390TRP |
| sulfatase/ARSA          | 7      |          |                 |           |
| Arylsulfatase A/steroid | 250100 | NM_00048 |                 | PHE398DEL |
| sulfatase/ARSA          | 7      |          |                 |           |
| Arylsulfatase A/steroid | 250100 | NM_00048 |                 | THR409ILE |
| sulfatase/ARSA          | 7      |          |                 |           |

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|                                           |        |               |                                        |
|-------------------------------------------|--------|---------------|----------------------------------------|
| Arylsulfatase A/steroid<br>sulfatase/ARSA | 250100 | NM_00048<br>7 | GLN486TER                              |
| Arylsulfatase A/steroid<br>sulfatase/ARSA | 250100 | NM_00048<br>7 | THR799GLY                              |
| Arylsulfatase A/steroid<br>sulfatase/ARSA | 250100 | NM_00048<br>7 | P148L                                  |
| Arylsulfatase A/steroid<br>sulfatase/ARSA | 250100 | NM_00048<br>7 | P191T                                  |
| Arylsulfatase A/steroid<br>sulfatase/ARSA | 250100 | NM_00048<br>7 | R496H                                  |
| Arylsulfatase A/steroid<br>sulfatase/ARSA | 250100 | NM_00048<br>7 | N350S                                  |
| Arylsulfatase A/steroid<br>sulfatase/ARSA | 250100 | NM_00048<br>7 | 9-bp deletion<br>(2320del9)<br>NlaIII1 |
| Arylsulfatase A/steroid<br>sulfatase/ARSA | 250100 | NM_00048<br>7 |                                        |
| Arylsulfatase A/steroid<br>sulfatase/ARSA | 250100 | NM_00048<br>7 | NlaIII2                                |
| Arylsulfatase A/steroid<br>sulfatase/ARSA | 250100 | NM_00048<br>7 | BsrI                                   |
| Arylsulfatase A/steroid<br>sulfatase/ARSA | 250100 | NM_00048<br>7 | BamHI                                  |
| Arylsulfatase A/steroid<br>sulfatase/ARSA | 250100 | NM_00048<br>7 |                                        |
| Arylsulfatase A/steroid<br>sulfatase/ARSA | 250100 | NM_00048<br>7 | L428P                                  |
| Arylsulfatase A/steroid<br>sulfatase/ARSA | 250100 | NM_00048<br>7 | I179S                                  |
| Arylsulfatase A/steroid<br>sulfatase/ARSA | 250100 | NM_00048<br>7 | R84Q                                   |
| Arylsulfatase A/steroid<br>sulfatase/ARSA | 250100 | NM_00048<br>7 | S96F                                   |
| Arylsulfatase A/steroid<br>sulfatase/ARSA | 250100 | NM_00048<br>7 | S95N                                   |

|                         |        |          |               |  |
|-------------------------|--------|----------|---------------|--|
| sulfatase/ARSA          | 7      |          |               |  |
| Arylsulfatase A/steroid | 250100 | NM_00048 | G119R         |  |
| sulfatase/ARSA          | 7      |          |               |  |
| Arylsulfatase A/steroid | 250100 | NM_00048 | D152Y         |  |
| sulfatase/ARSA          | 7      |          |               |  |
| Arylsulfatase A/steroid | 250100 | NM_00048 | R244H         |  |
| sulfatase/ARSA          | 7      |          |               |  |
| Arylsulfatase A/steroid | 250100 | NM_00048 | S250Y         |  |
| sulfatase/ARSA          | 7      |          |               |  |
| Arylsulfatase A/steroid | 250100 | NM_00048 | A314T         |  |
| sulfatase/ARSA          | 7      |          |               |  |
| Arylsulfatase A/steroid | 250100 | NM_00048 | R384C         |  |
| sulfatase/ARSA          | 7      |          |               |  |
| Arylsulfatase A/steroid | 250100 | NM_00048 | R496H         |  |
| sulfatase/ARSA          | 7      |          |               |  |
| Arylsulfatase A/steroid | 250100 | NM_00048 | K367N         |  |
| sulfatase/ARSA          | 7      |          |               |  |
| Arylsulfatase A/steroid | 250100 | NM_00048 | leu76pro      |  |
| sulfatase/ARSA          | 7      |          |               |  |
| Arylsulfatase A/steroid | 250100 | NM_00048 | A2725G        |  |
| sulfatase/ARSA          | 7      |          |               |  |
| Arylsulfatase A/steroid | 250100 | NM_00048 | A1788G        |  |
| sulfatase/ARSA          | 7      |          |               |  |
| Arylsulfatase A/steroid | 250100 | NM_00048 | D255H         |  |
| sulfatase/ARSA          | 7      |          |               |  |
| Arylsulfatase A/steroid | 250100 | NM_00048 | 287 C-->T     |  |
| sulfatase/ARSA          | 7      |          |               |  |
| Arylsulfatase A/steroid | 250100 | NM_00048 | 1524+95 A-->G |  |
| sulfatase/ARSA          | 7      |          |               |  |
| Arylsulfatase A/steroid | 250100 | NM_00048 | Q190-->H      |  |
| sulfatase/ARSA          | 7      |          |               |  |

|                                           |        |               |                             |
|-------------------------------------------|--------|---------------|-----------------------------|
| Arylsulfatase A/steroid<br>sulfatase/ARSA | 250100 | NM_00048<br>7 | A1788G                      |
| Arylsulfatase A/steroid<br>sulfatase/ARSA | 250100 | NM_00048<br>7 | A2723G                      |
| Arylsulfatase A/steroid<br>sulfatase/ARSA | 250100 | NM_00048<br>7 | C2330T                      |
| Arylsulfatase A/steroid<br>sulfatase/ARSA | 250100 | NM_00048<br>7 | 11-bp deletion in<br>exon 8 |
| Arylsulfatase A/steroid<br>sulfatase/ARSA | 250100 | NM_00048<br>7 | A1049G                      |
| Arylsulfatase A/steroid<br>sulfatase/ARSA | 250100 | NM_00048<br>7 | TaqI                        |
| Arylsulfatase A/steroid<br>sulfatase/ARSA | 250100 | NM_00048<br>7 | BamHI                       |
| Arylsulfatase B/steroid<br>sulfatase/ARSB | 253200 | NM_00004<br>6 | GLY137VAL                   |
| Arylsulfatase B/steroid<br>sulfatase/ARSB | 253200 | NM_00004<br>6 | CYS117ARG                   |
| Arylsulfatase B/steroid<br>sulfatase/ARSB | 253200 | NM_00004<br>6 | LEU236PRO                   |
| Arylsulfatase B/steroid<br>sulfatase/ARSB | 253200 | NM_00004<br>6 | CYS405TYR                   |
| Arylsulfatase B/steroid<br>sulfatase/ARSB | 253200 | NM_00004<br>6 | 1-BP DEL frameshift         |
| Arylsulfatase B/steroid<br>sulfatase/ARSB | 253200 | NM_00004<br>6 | 743C DEL frameshift         |
| Arylsulfatase B/steroid<br>sulfatase/ARSB | 253200 | NM_00004<br>6 | 11-BP DEL                   |
| Arylsulfatase B/steroid<br>sulfatase/ARSB | 253200 | NM_00004<br>6 | G302R                       |
| Arylsulfatase B/steroid<br>sulfatase/ARSB | 253200 | NM_00004<br>6 | Q456X                       |

|                         |        |          |                     |  |
|-------------------------|--------|----------|---------------------|--|
| sulfatase/ARSB          | 6      |          |                     |  |
| Arylsulfatase B/steroid | 253200 | NM_00004 | A1191G              |  |
| sulfatase/ARSB          | 6      |          |                     |  |
| Arylsulfatase B/steroid | 253200 | NM_00004 | *534Q               |  |
| sulfatase/ARSB          | 6      |          |                     |  |
| Arylsulfatase B/steroid | 253200 | NM_00004 | R160*               |  |
| sulfatase/ARSB          | 6      |          |                     |  |
| Arylsulfatase B/steroid | 253200 | NM_00004 | R160Q               |  |
| sulfatase/ARSB          | 6      |          |                     |  |
| Arylsulfatase B/steroid | 253200 | NM_00004 | 7-bp del frameshift |  |
| sulfatase/ARSB          | 6      |          |                     |  |
| Arylsulfatase B/steroid | 253200 | NM_00004 | deletion (delta     |  |
| sulfatase/ARSB          | 6      |          | G237-C243)          |  |
| Arylsulfatase B/steroid | 253200 | NM_00004 | R152W               |  |
| sulfatase/ARSB          | 6      |          |                     |  |
| Arylsulfatase B/steroid | 253200 | NM_00004 | arg144gly           |  |
| sulfatase/ARSB          | 6      |          |                     |  |
| Arylsulfatase B/steroid | 253200 | NM_00004 | arg192cys           |  |
| sulfatase/ARSB          | 6      |          |                     |  |
| Arylsulfatase B/steroid | 253200 | NM_00004 | pro321leu           |  |
| sulfatase/ARSB          | 6      |          |                     |  |
| Arylsulfatase B/steroid | 253200 | NM_00004 | insertion between   |  |
| sulfatase/ARSB          | 6      |          | T1284 and G1285     |  |
| Arylsulfatase B/steroid | 253200 | NM_00004 | deletion C1577      |  |
| sulfatase/ARSB          | 6      |          |                     |  |
| Arylsulfatase B/steroid | 253200 | NM_00004 | T1600C              |  |
| sulfatase/ARSB          | 6      |          |                     |  |
| Arylsulfatase C,        | 308100 | NM_00035 | TRP372ARG           |  |
| isozyme s/steroid       | 1      |          |                     |  |
| sulfatase/ARCS1         |        |          |                     |  |
| Arylsulfatase C,        | 308100 | NM_00035 | CYS446TYR           |  |

|                                                          |        |               |                                                   |
|----------------------------------------------------------|--------|---------------|---------------------------------------------------|
| isozyme s/steroid<br>sulfatase/ARCS1                     | 308100 | NM_00035<br>1 | SER341LEU                                         |
| isozyme s/steroid<br>sulfatase/ARCS1                     | 308100 | NM_00035<br>1 | TRP372PRO                                         |
| Arylsulfatase C,<br>isozyme s/steroid<br>sulfatase/ARCS1 | 308100 | NM_00035<br>1 | HIS444ARG                                         |
| Arylsulfatase C,<br>isozyme s/steroid<br>sulfatase/ARCS1 | 308100 | NM_00035<br>1 | 19-bp insertion 1477 frameshift<br>intron/exon 18 |
| Arylsulfatase D/steroid<br>sulfatase/ARSD                | 300002 | *****         | none found                                        |
| Arylsulfatase E/steroid<br>sulfatase/ARSE                | 300180 | NM_00004<br>7 | ARG12SER                                          |
| Arylsulfatase E/steroid<br>sulfatase/ARSE                | 300180 | NM_00004<br>7 | GLY117ARG                                         |
| Arylsulfatase E/steroid<br>sulfatase/ARSE                | 300180 | NM_00004<br>7 | ARG111PRO                                         |
| Arylsulfatase E/steroid<br>sulfatase/ARSE                | 300180 | NM_00004<br>7 | GLY137VAL                                         |
| Arylsulfatase E/steroid<br>sulfatase/ARSE                | 300180 | NM_00004<br>7 | GLY245ARG                                         |
| Arylsulfatase E/steroid<br>sulfatase/ARSE                | 300180 | NM_00004<br>7 | CYS492TYR                                         |
| Arylsulfatase F/steroid<br>sulfatase/ARSF                | 300003 | NM_00404<br>2 | none found                                        |
| bile salt export                                         | 603201 | NM_00374      | ARG575TER                                         |

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|                                                            |        |               |                                   |
|------------------------------------------------------------|--------|---------------|-----------------------------------|
| butyrylcholinesterase<br>1/serum cholinesterase<br>1/BCHE1 | 177400 | NM_00005<br>5 | G365R                             |
| butyrylcholinesterase<br>1/serum cholinesterase<br>1/BCHE1 | 177400 | NM_00005<br>5 | Q119X                             |
| butyrylcholinesterase<br>1/serum cholinesterase<br>1/BCHE1 | 177400 | NM_00005<br>5 | R515C                             |
| butyrylcholinesterase<br>1/serum cholinesterase<br>1/BCHE1 | 177400 | NM_00005<br>5 | GLU497VAL                         |
| butyrylcholinesterase<br>1/serum cholinesterase<br>1/BCHE1 | 177400 | NM_00005<br>5 | THR243MET                         |
| butyrylcholinesterase<br>1/serum cholinesterase<br>1/BCHE1 | 177400 | NM_00005<br>5 | GGT-to-GGAG Gly 117<br>Frameshift |
| butyrylcholinesterase<br>1/serum cholinesterase<br>1/BCHE1 | 177400 | NM_00005<br>5 | Gly115 by Asp                     |
| butyrylcholinesterase<br>1/serum cholinesterase<br>1/BCHE1 | 177400 | NM_00005<br>5 | 342-bp Alu in exon two            |
| butyrylcholinesterase<br>1/serum cholinesterase<br>1/BCHE1 | 177400 | NM_00005<br>5 | 209 A/G Asp-70 to Gly             |
| butyrylcholinesterase<br>1/serum cholinesterase<br>1/BCHE1 | 177400 | NM_00005<br>5 |                                   |
| CARBOXYLESTERA                                             | 114835 |               | none found                        |

## SE 1; CES1

|                                                                  |        |        |                           |              |
|------------------------------------------------------------------|--------|--------|---------------------------|--------------|
| Catechol-O-Methyltransferase                                     | 116790 | M58525 | BglI                      |              |
| Catechol-O-Methyltransferase                                     | 116790 | M58525 | 186C > T at exon 3        |              |
| Catechol-O-Methyltransferase                                     | 116790 | M58525 | 408C > G at exon 4        |              |
| Catechol-O-Methyltransferase                                     | 116790 | M58525 | 472G > A at exon 4        |              |
| Catechol-O-Methyltransferase                                     | 116790 | M58525 | 597G > A at exon 5        |              |
| Catechol-O-Methyltransferase                                     | 116790 | M58525 | 821-827insC at the 3'     |              |
| Catechol-O-Methyltransferase                                     | 116790 | M58525 |                           | Val158-->Met |
| Catechol-O-Methyltransferase                                     | 116790 | M58525 | NlaIII                    |              |
| Catechol-O-Methyltransferase                                     | 116790 | M58525 | MspI                      |              |
| Catechol-O-Methyltransferase                                     | 116790 | M58525 |                           | val-108-met  |
| Catechol-O-Methyltransferase                                     | 116790 | M58525 | G/A1947                   |              |
| Catechol-O-Methyltransferase                                     | 116790 | M58525 | C256G silent              |              |
| Catechol-O-Methyltransferase                                     | 100640 | M26761 | none found                |              |
| class I aldehyde dehydrogenase cytochrome P450 aromatase (CYP19) | 107910 | X13589 | (TTTA)n in intron 5       |              |
| cytochrome P450 aromatase (CYP19)                                | 107910 | X13589 | 1-BP DEL, 408C frameshift |              |



|                                                                                           |        |               |                                                          |
|-------------------------------------------------------------------------------------------|--------|---------------|----------------------------------------------------------|
| cytochrome P450<br>aromatase (CYP19)                                                      | 107910 | X13589        | G-->A at Val80 silent                                    |
| cytochrome P450<br>aromatase (CYP19)                                                      | 107910 | X13589        | G-1094 -A ARG365GLN                                      |
| cytochrome P450<br>aromatase (CYP19)                                                      | 107910 | X13589        | G-to-A Val370-to-Met                                     |
| cytochrome P450<br>aromatase (CYP19)                                                      | 107910 | X13589        | GT to AT exon and<br>intron 3                            |
| cytochrome P450<br>aromatase (CYP19)                                                      | 107910 | X13589        | splice donor 29 extra amino<br>(GT>GC) of intron 6 acids |
| cytochrome P450<br>aromatase (CYP19)                                                      | 107910 | X13589        | Arg264cys                                                |
| cytochrome P450<br>aromatase (CYP19)                                                      | 107910 | X13589        | ARG375CYS                                                |
| cytochrome P450<br>aromatase (CYP19)                                                      | 107910 | X13589        | ARG435CYS                                                |
| cytochrome P450<br>aromatase (CYP19)                                                      | 107910 | X13589        | CYS437TYR                                                |
| cytochrome P450,<br>subfamily I,<br>polypeptide 1 (aryl<br>hydrocarbon<br>oxidase)/CYP1A1 | 108330 | NM_00049<br>9 | cATT-GTT Ile462Val                                       |
| cytochrome P450,<br>subfamily I,<br>polypeptide 1 (aryl<br>hydrocarbon<br>oxidase)/CYP1A1 | 108330 | NM_00049<br>9 | MspI                                                     |
| cytochrome P450,<br>subfamily I,<br>polypeptide 1 (aryl<br>hydrocarbon<br>oxidase)/CYP1A1 | 108330 | NM_00049<br>9 | T6235C                                                   |

|                                                                                                                                                                                                                                                              |        |                       |           |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------|-----------------------|-----------|
| hydrocarbon<br>oxidase)/CYP1A1<br>cytochrome P450,<br>subfamily I,<br>polypeptide 1 (aryl<br>hydrocarbon<br>oxidase)/CYP1A1<br>cytochrome P450,<br>subfamily I,<br>polypeptide 1 (aryl<br>hydrocarbon<br>oxidase)/CYP1A1<br>cytochrome P450,<br>subfamily I, | 108330 | NM_00049 <sub>9</sub> | A4889G    |
| hydrocarbon<br>oxidase)/CYP1A1<br>cytochrome P450,<br>subfamily I,<br>polypeptide 1 (aryl<br>hydrocarbon<br>oxidase)/CYP1A1<br>cytochrome P450,<br>subfamily I,                                                                                              | 108330 | NM_00049 <sub>9</sub> | T5639C    |
| hydrocarbon<br>oxidase)/CYP1A1<br>cytochrome P450,<br>subfamily I,<br>polypeptide 1 (aryl<br>hydrocarbon<br>oxidase)/CYP1A1<br>cytochrome P450,<br>subfamily I,                                                                                              | 108330 | NM_00049 <sub>9</sub> | C4887A    |
| hydrocarbon<br>oxidase)/CYP1A1<br>cytochrome P450,<br>subfamily I,<br>polypeptide 1 (aryl<br>hydrocarbon<br>oxidase)/CYP1A1<br>cytochrome P450,<br>subfamily I,                                                                                              | 108330 | NM_00049 <sub>9</sub> | C(-459)T  |
| hydrocarbon<br>oxidase)/CYP1A1<br>cytochrome P450,<br>subfamily I,<br>polypeptide 1 (aryl<br>hydrocarbon<br>oxidase)/CYP1A1<br>cytochrome P450,<br>subfamily I,                                                                                              | 108330 | NM_00049 <sub>9</sub> | G(-469)A  |
| hydrocarbon<br>oxidase)/CYP1A1<br>cytochrome P450,<br>subfamily I,<br>polypeptide 1 (aryl<br>hydrocarbon<br>oxidase)/CYP1A1<br>cytochrome P450,<br>subfamily I,                                                                                              | 108330 | NM_00049 <sub>9</sub> | C(4151)T) |

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |        |               |                                               |  |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------|---------------|-----------------------------------------------|--|
| oxidase)/CYP1A1<br>cytochrome P450,<br>subfamily I,<br>polypeptide 1 (aryl<br>hydrocarbon<br>oxidase)/CYP1A1<br>cytochrome P450,<br>subfamily I,<br>polypeptide 2<br>(phenacetin<br>metabolism)/CYP1A2<br>cytochrome P450,<br>subfamily I,<br>polypeptide 2<br>(phenacetin<br>metabolism)/CYP1A2<br>cytochrome P450,<br>subfamily I,<br>polypeptide 2<br>(phenacetin<br>metabolism)/CYP1A2<br>cytochrome P450,<br>subfamily I,<br>polypeptide 2<br>(phenacetin<br>metabolism)/CYP1A2<br>cytochrome P450,<br>subfamily IB,<br>polypeptide 1 (dioxin<br>inducible)/CYP1B1<br>cytochrome P450,<br>subfamily IB,<br>polypeptide 1 (dioxin<br>inducible)/CYP1B1<br>cytochrome P450,<br>subfamily IB, | 108330 | NM_00049<br>9 | HinCII                                        |  |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 | 124060 | AH002667      | C-->A<br>polymorphism in<br>intron 1          |  |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 | 124060 | AH002667      | G->A -2964                                    |  |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 | 124060 | AH002667      | F21L                                          |  |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 | 601771 | NM_00010<br>4 | deletion 1410 to frameshift<br>1422           |  |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 | 601771 | NM_00010<br>4 | insertion between frameshift<br>1209 and 1214 |  |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 | 601771 | NM_00010<br>4 | GLY61GLU                                      |  |

|                                                                        |        |           |                      |
|------------------------------------------------------------------------|--------|-----------|----------------------|
| polypeptide 1 (dioxin inducible)/CYP1B1 cytochrome P450, subfamily IB, | 601771 | NM_000104 | 1546DUP10 frameshift |
| polypeptide 1 (dioxin inducible)/CYP1B1 cytochrome P450, subfamily IB, | 601771 | NM_000104 | GLY365TRP            |
| polypeptide 1 (dioxin inducible)/CYP1B1 cytochrome P450, subfamily IB, | 601771 | NM_000104 | ARG469TRP            |
| polypeptide 1 (dioxin inducible)/CYP1B1 cytochrome P450, subfamily IB, | 601771 | NM_000104 | ASP374ASN            |
| polypeptide 1 (dioxin inducible)/CYP1B1 cytochrome P450, subfamily IB, | 601771 | NM_000104 | LYS387GLU            |
| polypeptide 1 (dioxin inducible)/CYP1B1 cytochrome P450, subfamily IB, | 601771 | NM_000104 | 432 (Val-->Leu)      |
| polypeptide 1 (dioxin inducible)/CYP1B1 cytochrome P450, subfamily IB, | 601771 | NM_000104 | 453 (Asn-->Ser)      |
| polypeptide 1 (dioxin inducible)/CYP1B1 cytochrome P450,               | 123960 | X13897    | Xmnl                 |

|                                                                                                                                                                    |        |                |             |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------|----------------|-------------|
| subfamily II,<br>polypeptide 1<br>(phenobarbital<br>inducible)/CYP2A<br>cytochrome P450,<br>subfamily IIA,<br>polypeptide 6<br>(coumarin-7-<br>hydroxylase)/CYP2A6 | 122720 | NM_00076<br>_2 | LEU160HIS   |
| cytochrome P450,<br>subfamily IIA,<br>polypeptide 6<br>(coumarin-7-<br>hydroxylase)/CYP2A6                                                                         | 122720 | NM_00076<br>_2 | CYP2A6 null |
| cytochrome P450,<br>subfamily IIA,<br>polypeptide 6<br>(coumarin-7-<br>hydroxylase)/CYP2A6                                                                         | 122720 | NM_00076<br>_2 | Ddel        |
| cytochrome P450,<br>subfamily IIB<br>(phenobarbital<br>inducible)/CYP2B<br>cytochrome P450,<br>subfamily IIC,<br>polypeptide<br>18/CYP2C18                         | 123930 | M29874         | none found  |
| cytochrome P450,<br>subfamily IIC,<br>polypeptide<br>18/CYP2C18                                                                                                    | 601131 | *****          | T204 --> A  |
| cytochrome P450,<br>subfamily IIC,<br>polypeptide<br>18/CYP2C18                                                                                                    | 601131 | *****          | A-460 --> T |

|                                                                                                 |        |               |           |           |
|-------------------------------------------------------------------------------------------------|--------|---------------|-----------|-----------|
| cytochrome P450,<br>subfamily IIC,<br>polypeptide<br>18/CYP2C18                                 | 601131 | *****         | Ddel      |           |
| cytochrome P450,<br>subfamily IIC,<br>polypeptide<br>18/CYP2C18                                 | 601131 | *****         |           | Thr385Met |
| cytochrome P450,<br>subfamily IIC,<br>polypeptide 19<br>(mephenytoin 4-<br>hydroxylase)/CYP2C1  | 124020 | NM_00076<br>9 | 40-BP DEL |           |
| cytochrome P450,<br>subfamily IIC,<br>polypeptide 19<br>(mephenytoin 4-<br>hydroxylase)/CYP2C1  | 124020 | NM_00076<br>9 |           | ARG433TRP |
| cytochrome P450,<br>subfamily IIC,<br>polypeptide 9<br>(hydroxylation of<br>tolbutamide)/CYP2C9 | 601129 | *****         |           |           |
| cytochrome P450,<br>subfamily IIC,<br>polypeptide 9                                             | 601130 | *****         |           | ILE359LEU |
| cytochrome P450,<br>subfamily IIC,<br>polypeptide 9                                             | 601130 | *****         |           | ARG144CYS |

|                                                                                                                                             |        |               |                                                                                                                |
|---------------------------------------------------------------------------------------------------------------------------------------------|--------|---------------|----------------------------------------------------------------------------------------------------------------|
| (hydroxylation of<br>tolbutamide)/CYP2C9<br>cytochrome P450,<br>subfamily IIC,<br>polypeptide 9<br>(hydroxylation of<br>tolbutamide)/CYP2C9 | 601130 | *****         | Tyr358/Cys                                                                                                     |
| cytochrome P450,<br>subfamily IIC,<br>polypeptide 9<br>(hydroxylation of<br>tolbutamide)/CYP2C9                                             | 601130 | *****         | Gly417/Asp                                                                                                     |
| cytochrome P450,<br>subfamily IID,<br>polypeptide 6<br>(debrisoquine<br>hydroxylation)/CYP2D<br>6                                           | 124030 | NM_00010<br>6 | G>C Glutamine<br>intron splice site<br>Histidine<br>(splicing defect;<br>does not splice<br>intron at 3' site) |
| cytochrome P450,<br>subfamily IID,<br>polypeptide 6<br>(debrisoquine<br>hydroxylation)/CYP2D<br>6                                           | 124030 | NM_00010<br>6 | G>A Glycine intron<br>splice site<br>Arginine<br>(splicing defect;<br>does not splice<br>intron at 3' site)    |
| cytochrome P450,<br>subfamily IID,<br>polypeptide 6<br>(debrisoquine<br>hydroxylation)/CYP2D<br>6                                           | 124030 | NM_00010<br>6 | G>C Valine 136<br>Valine                                                                                       |
| cytochrome P450,<br>subfamily IID,<br>polypeptide 6<br>(debrisoquine<br>hydroxylation)/CYP2D<br>6                                           | 124030 | NM_00010      | G>C Serine 486                                                                                                 |

|                                                                                                   |                      |                                                                                                  |
|---------------------------------------------------------------------------------------------------|----------------------|--------------------------------------------------------------------------------------------------|
| subfamily IID,<br>polypeptide 6<br>(debrisoquine<br>hydroxylation)/CYP2D<br>6                     | 6                    | Threonine                                                                                        |
| cytochrome P450,<br>subfamily IID,<br>polypeptide 6<br>(debrisoquine<br>hydroxylation)/CYP2D<br>6 | 124030 NM_00010<br>6 | insertion Arginine<br>(A)>deletion (A) Glycine<br>(frameshift -<br>premature stop<br>next codon) |
| cytochrome P450,<br>subfamily IID,<br>polypeptide 6<br>(debrisoquine<br>hydroxylation)/CYP2D<br>6 | 124030 NM_00010<br>6 | A>C Histidine 324<br>Proline                                                                     |
| cytochrome P450,<br>subfamily IID,<br>polypeptide 6<br>(debrisoquine<br>hydroxylation)/CYP2D<br>6 | 124030 NM_00010<br>6 | G>T Glycine 169<br>Stop Codon                                                                    |
| cytochrome P450,<br>subfamily IID,<br>polypeptide 6<br>(debrisoquine<br>hydroxylation)/CYP2D<br>6 | 124030 NM_00010<br>6 | G>A Glycine 42<br>Arginine                                                                       |
| cytochrome P450,<br>subfamily IID,<br>polypeptide 6<br>(debrisoquine<br>hydroxylation)/CYP2D<br>6 | 124030 NM_00010<br>6 | insertion Tryptophan<br>(T)>deletion (T) Glycine                                                 |



|                                                                                                   |        |               |                                                                                   |
|---------------------------------------------------------------------------------------------------|--------|---------------|-----------------------------------------------------------------------------------|
| polypeptide 6<br>(debrisoquine<br>hydroxylation)/CYP2D<br>6                                       |        |               | (frameshift -<br>premature stop<br>at next codon)                                 |
| cytochrome P450,<br>subfamily IID,<br>polypeptide 6<br>(debrisoquine<br>hydroxylation)/CYP2D<br>6 | 124030 | NM_00010<br>6 | C>T Arginine 296<br>Cysteine                                                      |
| cytochrome P450,<br>subfamily IID,<br>polypeptide 6<br>(debrisoquine<br>hydroxylation)/CYP2D<br>6 | 124030 | NM_00010<br>6 | C>T Proline 34<br>Serine                                                          |
| cytochrome P450,<br>subfamily IID,<br>polypeptide 6<br>(debrisoquine<br>hydroxylation)/CYP2D<br>6 | 124030 | NM_00010<br>6 | Deletion Leucine<br>(T)>Insertion (T) Leucine<br>(frameshift -<br>premature stop) |
| cytochrome P450,<br>subfamily IID,<br>polypeptide 6<br>(debrisoquine<br>hydroxylation)/CYP2D<br>6 | 124030 | NM_00010<br>6 | G>A Serine 401<br>Serine                                                          |
| cytochrome P450,<br>subfamily IID,<br>polypeptide 6<br>(debrisoquine<br>hydroxylation)/CYP2D<br>6 | 124030 | NM_00010<br>6 | G AA>deletion Lysine 281<br>Lysine deletion                                       |

|                                                                                                   |        |               |                                             |
|---------------------------------------------------------------------------------------------------|--------|---------------|---------------------------------------------|
| (debrisoquine<br>hydroxylation)/CYP2D<br>6                                                        | 124030 | NM_00010<br>6 | A>G Histidine 94<br>Arginine                |
| cytochrome P450,<br>subfamily IID,<br>polypeptide 6<br>(debrisoquine<br>hydroxylation)/CYP2D<br>6 | 124030 | NM_00010<br>6 | T>C Leucine 421<br>Proline                  |
| cytochrome P450,<br>subfamily IID,<br>polypeptide 6<br>(debrisoquine<br>hydroxylation)/CYP2D<br>6 | 124030 | NM_00010<br>6 | AG A>deletion Lysine 281<br>Lysine deletion |
| cytochrome P450,<br>subfamily IID,<br>polypeptide 6<br>(debrisoquine<br>hydroxylation)/CYP2D<br>6 | 124030 | NM_00010<br>6 | C>G Threonine 98<br>Threonine               |
| cytochrome P450,<br>subfamily IID,<br>polypeptide 6<br>(debrisoquine<br>hydroxylation)/CYP2D<br>6 | 124030 | NM_00010<br>6 | C>G Leucine 91<br>Valine                    |

|                                                                                                   |        |               |                                           |
|---------------------------------------------------------------------------------------------------|--------|---------------|-------------------------------------------|
| hydroxylation)/CYP2D<br>6                                                                         | 124030 | NM_00010<br>6 | G>A Glycine 212<br>Glutamic acid          |
| cytochrome P450,<br>subfamily IID,<br>polypeptide 6<br>(debrisoquine<br>hydroxylation)/CYP2D<br>6 | 124030 | NM_00010<br>6 | C>T Phenylalanine<br>112<br>Phenylalanine |
| cytochrome P450,<br>subfamily IIE (ethanol<br>inducible)/CYP2E<br>6                               | 124040 | J02843        | (GGAT)n.(CCTA)n<br>repeat element intron  |
| cytochrome P450,<br>subfamily IIE (ethanol<br>inducible)/CYP2E<br>6                               | 124040 | J02843        | MspI                                      |
| cytochrome P450,<br>subfamily IIE (ethanol<br>inducible)/CYP2E<br>6                               | 124040 | J02843        | PstI                                      |
| cytochrome P450,<br>subfamily IIE (ethanol<br>inducible)/CYP2E<br>6                               | 124040 | J02843        | RsaI                                      |
| cytochrome P450,<br>subfamily IIE (ethanol<br>inducible)/CYP2E<br>6                               | 124040 | J02843        | XmnI                                      |
| cytochrome P450,<br>subfamily IIE (ethanol<br>inducible)/CYP2E<br>6                               | 124040 | J02843        | Taq I                                     |

|                                                                                                                     |        |               |              |                                   |
|---------------------------------------------------------------------------------------------------------------------|--------|---------------|--------------|-----------------------------------|
| inducible)/CYP2E<br>cytochrome P450,<br>subfamily IIF<br>(ethoxycoumarin<br>monooxygenase),<br>polypeptide 1/CYP2F1 | 124070 | NM_00077<br>4 | none found   |                                   |
| cytochrome P450,<br>subfamily IIIA<br>(niphedipine oxidase),<br>polypeptide 3/CYP3A3                                | 124010 | NM_00077<br>6 | a-g PROMOTER |                                   |
| cytochrome P450,<br>subfamily IIIA<br>(niphedipine oxidase),<br>polypeptide 3/CYP3A3                                | 124010 | NM_00077<br>6 | -292 a-g     |                                   |
| cytochrome P450,<br>subfamily IIIA<br>(niphedipine oxidase),<br>polypeptide 3/CYP3A3                                | 124010 | NM_00077<br>6 |              | Thr431Ile                         |
| cytochrome P450,<br>subfamily IIIA<br>(niphedipine oxidase),<br>polypeptide 3/CYP3A3                                | 124010 | NM_00077<br>6 |              | Trp392Val                         |
| cytochrome P450,<br>subfamily IIIA<br>(niphedipine oxidase),<br>polypeptide 3/CYP3A3                                | 124010 | NM_00077<br>6 |              | Ile224 replacing<br>Thr224-Val225 |
| Dehydroepiandrosteron<br>e (DHEA)-preferring<br>sulfotransferase, family<br>2A, member<br>1/SULT2A1                 | 125263 | NM_00316<br>7 |              | Met 57 --> Thr                    |

|                                                                                                                                                          |        |           |                     |
|----------------------------------------------------------------------------------------------------------------------------------------------------------|--------|-----------|---------------------|
| Dehydroepiandrosterone (DHEA)-preferring sulfotransferase, family 2A, member 1/SULT2A1                                                                   | 125263 | NM_003167 | Glu 186 --> Val     |
| Dihydrolipoamide dehydrogenase (E3 component of pyruvate dehydrogenase complex, 2-oxo-glutarate complex, branched chain keto acid dehydrogenase complex) | 246900 | J03490    | LYS37GLU            |
| Dihydrolipoamide dehydrogenase (E3 component of pyruvate dehydrogenase complex, 2-oxo-glutarate complex, branched chain keto acid dehydrogenase complex) | 246900 | J03490    | PRO453LEU           |
| Dihydrolipoamide dehydrogenase (E3 component of pyruvate dehydrogenase complex, 2-oxo-glutarate complex, branched chain keto acid dehydrogenase complex) | 246900 | J03490    | 1-BP INS frameshift |

|                                                                                                                                                                                                                                                                                  |        |          |           |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------|----------|-----------|
| complex)<br>Dihydrolipoamide<br>dehydrogenase (E3<br>component of pyruvate<br>dehydrogenase<br>complex, 2-oxo-<br>glutarate complex,<br>branched chain keto<br>acid dehydrogenase<br>complex)                                                                                    | 246900 | J03490   | GLY229CYS |
| Dihydrolipoamide<br>dehydrogenase (E3<br>component of pyruvate<br>dehydrogenase<br>complex, 2-oxo-<br>glutarate complex,<br>branched chain keto<br>acid dehydrogenase<br>complex)                                                                                                | 246900 | J03490   | Y35X      |
| Dihydrolipoamide<br>dehydrogenase (E3<br>component of pyruvate<br>dehydrogenase<br>complex)<br>Dihydrolipoamide<br>dehydrogenase (E3<br>component of pyruvate<br>dehydrogenase<br>complex, 2-oxo-<br>glutarate complex,<br>branched chain keto<br>acid dehydrogenase<br>complex) | 246900 | J03490   | R460G     |
| Dihydrolipoamide S-<br>acetyltransferase (E2<br>component of pyruvate                                                                                                                                                                                                            | 245349 | AF001437 | 85-BP DEL |

|                                                                                       |        |          |                            |  |  |
|---------------------------------------------------------------------------------------|--------|----------|----------------------------|--|--|
| dehydrogenase complex)                                                                |        |          |                            |  |  |
| Dihydrolipoamide S-acetyltransferase (E2 component of pyruvate dehydrogenase complex) | 245349 | AF001437 | 69-BP DEL                  |  |  |
| Dihydrolipoamide S-acetyltransferase (E2 component of pyruvate dehydrogenase complex) | 245349 | AF001437 | 4-BP DEL                   |  |  |
| dihydropyrimidine dehydrogenase DPD                                                   | 274270 | U09178   | deltaC1897                 |  |  |
| dihydropyrimidine dehydrogenase DPD                                                   | 274270 | U09178   | Arg21Gln                   |  |  |
| dihydropyrimidine dehydrogenase DPD                                                   | 274270 | U09178   | Val335Leu                  |  |  |
| dihydropyrimidine dehydrogenase DPD                                                   | 274270 | U09178   | Glu386Ter                  |  |  |
| dihydropyrimidine dehydrogenase DPD                                                   | 274270 | U09178   | 165-BP DEL                 |  |  |
| dihydropyrimidine dehydrogenase DPD                                                   | 274270 | U09178   | Ser534Asn                  |  |  |
| dihydropyrimidine dehydrogenase DPD                                                   | 274270 | U09178   | Ile543Val                  |  |  |
| dihydropyrimidine dehydrogenase DPD                                                   | 274270 | U09178   | Val732Ile                  |  |  |
| dihydropyrimidine dehydrogenase DPD                                                   | 274270 | U09178   | 4-BP DEL 296 to 299 (TCAT) |  |  |
| dihydropyrimidine dehydrogenase DPD                                                   | 274270 | U09178   | 1-BP DEL, 1897C Frameshift |  |  |

|                                              |        |           |                                      |
|----------------------------------------------|--------|-----------|--------------------------------------|
| dehydrogenase DPD                            | 274270 | U09178    | ARG886HIS                            |
| dihydropyrimidine                            |        |           |                                      |
| dehydrogenase DPD                            | 274270 | U09178    | CYS29ARG                             |
| dihydropyrimidine                            |        |           |                                      |
| dehydrogenase DPD                            | 274270 | U09178    | ASP974VAL                            |
| dihydropyrimidine                            |        |           |                                      |
| dehydrogenase DPD                            | 126455 | L24178    | 5' TaqI RFLP                         |
| Dopamine Transporter/<br>DAT1                |        |           |                                      |
| Dopamine Transporter/<br>DAT1                | 126455 | L24178    | 9-repeat allele                      |
| Dopamine Transporter/<br>DAT1                | 126455 | L24178    | 40-bp VNTR in the<br>3'-untranslated |
| eosinophil<br>peroxidase/EPX                 | 131399 |           | ARG286HIS                            |
| eosinophil<br>peroxidase/EPX                 | 131399 |           | INS G, NT1537                        |
| epoxide hydrolase<br>1/EPHX1<br>(microsomal) | 132810 | NM_000120 | TYR113HIS                            |
| epoxide hydrolase<br>1/EPHX1<br>(microsomal) | 132810 | NM_000120 | Exon 3 T to C                        |
| epoxide hydrolase<br>1/EPHX1<br>(microsomal) | 132810 | NM_000120 | His/Arg 139                          |
| epoxide hydrolase<br>2/EPHX2 (cytosolic)     | 132811 | *****     | none found                           |
| ESTERASE A-4                                 | 133220 |           | none found                           |
| ESTERASE A-5;<br>ESA5                        | 133230 |           | none found                           |



|                                             |        |            |                                    |            |
|---------------------------------------------|--------|------------|------------------------------------|------------|
| ESTERASE B                                  | 133260 |            | none found                         |            |
| ESTERASE B3; ESB3                           | 133290 |            | none found                         |            |
| ESTERASE C                                  | 133270 |            | none found                         |            |
| Estrogen-preferring<br>sulfotransferase/STE | 600043 | NM_00542_0 | none found                         |            |
| familial intrahepatic<br>cholestasis 1/FIC1 | 602397 | NM_00560_3 |                                    | GLY308VAL  |
| familial intrahepatic<br>cholestasis 1/FIC1 | 602397 | NM_00560_3 |                                    | GLY892ARG  |
| familial intrahepatic<br>cholestasis 1/FIC1 | 602397 | NM_00560_3 |                                    | LEU288SER  |
| familial intrahepatic<br>cholestasis 1/FIC1 | 602397 | NM_00560_3 | 2097T-C, +2 splice variant         |            |
| familial intrahepatic<br>cholestasis 1/FIC1 | 602397 | NM_00560_3 |                                    | 1.4-KB DEL |
| familial intrahepatic<br>cholestasis 1/FIC1 | 602397 | NM_00560_3 |                                    | ILE661THR  |
| familial intrahepatic<br>cholestasis 1/FIC1 | 602397 | NM_00560_3 | 9-BP DEL deletion GNR<br>(795-797) |            |
| folypolyglutamate<br>synthetase FPGS        | 136510 | M98045     | none found                         |            |
| gamma-glutamyl<br>hydrolase GGH             | 601509 | U55206     | none found                         |            |
| GAMMA-<br>GLUTAMYLTRANSF<br>ERASE 2         | 137181 |            | none found                         |            |
| Glucose-6-phosphate<br>dehydrogenase        | 305900 | X03674     |                                    | ASN126ASP  |
| Glucose-6-phosphate<br>dehydrogenase        | 305900 | X03674     |                                    | VAL68MET   |
| Glucose-6-phosphate                         | 305900 | X03674     |                                    | ASN126ASP  |

|                     |        |        |             |
|---------------------|--------|--------|-------------|
| dehydrogenase       | 305900 | X03674 | ALA335THR   |
| Glucose-6-phosphate |        |        |             |
| dehydrogenase       | 305900 | X03674 | GLU156LYS   |
| Glucose-6-phosphate |        |        |             |
| dehydrogenase       | 305900 | X03674 | GLY163SER   |
| Glucose-6-phosphate |        |        |             |
| dehydrogenase       | 305900 | X03674 | SER188PHE   |
| Glucose-6-phosphate |        |        |             |
| dehydrogenase       | 305900 | X03674 | ASP58ASN    |
| Glucose-6-phosphate |        |        |             |
| dehydrogenase       | 305900 | X03674 | ARG393HIS   |
| Glucose-6-phosphate |        |        |             |
| dehydrogenase       | 305900 | X03674 | GLY447ARG   |
| Glucose-6-phosphate |        |        |             |
| dehydrogenase       | 305900 | X03674 | ASP282HIS   |
| Glucose-6-phosphate |        |        |             |
| dehydrogenase       | 305900 | X03674 | PHE216LEU   |
| Glucose-6-phosphate |        |        |             |
| dehydrogenase       | 305900 | X03674 | LYS386GLU   |
| Glucose-6-phosphate |        |        |             |
| dehydrogenase       | 305900 | X03674 | ARG387HIS   |
| Glucose-6-phosphate |        |        |             |
| dehydrogenase       | 305900 | X03674 | CYS385ARG   |
| Glucose-6-phosphate |        |        |             |
| dehydrogenase       | 305900 | X03674 | GLY410CYS   |
| Glucose-6-phosphate |        |        |             |
| dehydrogenase       | 305900 | X03674 | ARG285HIS   |
| Glucose-6-phosphate |        |        |             |
| dehydrogenase       | 305900 | X03674 | NT1116, G-A |
| Glucose-6-phosphate |        |        |             |
| dehydrogenase       |        |        |             |

|                                      |        |        |               |           |
|--------------------------------------|--------|--------|---------------|-----------|
| Glucose-6-phosphate<br>dehydrogenase | 305900 | X03674 | NT1311, C-T   |           |
| Glucose-6-phosphate<br>dehydrogenase | 305900 | X03674 | EX6, -60, C-G |           |
| Glucose-6-phosphate<br>dehydrogenase | 305900 | X03674 |               | ARG454HIS |
| Glucose-6-phosphate<br>dehydrogenase | 305900 | X03674 |               | ARG459LEU |
| Glucose-6-phosphate<br>dehydrogenase | 305900 | X03674 |               | GLU398LYS |
| Glucose-6-phosphate<br>dehydrogenase | 305900 | X03674 |               | ASP181VAL |
| Glucose-6-phosphate<br>dehydrogenase | 305900 | X03674 |               | ASN126ASP |
| Glucose-6-phosphate<br>dehydrogenase | 305900 | X03674 |               | VAL213LEU |
| Glucose-6-phosphate<br>dehydrogenase | 305900 | X03674 |               | ARG393HIS |
| Glucose-6-phosphate<br>dehydrogenase | 305900 | X03674 |               | VAL291MET |
| Glucose-6-phosphate<br>dehydrogenase | 305900 | X03674 |               | ARG227LEU |
| Glucose-6-phosphate<br>dehydrogenase | 305900 | X03674 |               | LEU323PRO |
| Glucose-6-phosphate<br>dehydrogenase | 305900 | X03674 |               | ARG463HIS |
| Glucose-6-phosphate<br>dehydrogenase | 305900 | X03674 |               | ASN363LYS |
| Glucose-6-phosphate<br>dehydrogenase | 305900 | X03674 |               | ARG198CYS |
| Glucose-6-phosphate<br>dehydrogenase | 305900 | X03674 |               | SER106CYS |

|                     |        |        |           |
|---------------------|--------|--------|-----------|
| dehydrogenase       | 305900 | X03674 | ARG182TRP |
| Glucose-6-phosphate | 305900 | X03674 | ARG198CYS |
| dehydrogenase       | 305900 | X03674 | ASN165ASP |
| Glucose-6-phosphate | 305900 | X03674 | ARG198PRO |
| dehydrogenase       | 305900 | X03674 | ARG227GLN |
| Glucose-6-phosphate | 305900 | X03674 | PRO353SER |
| dehydrogenase       | 305900 | X03674 | ARG387CYS |
| Glucose-6-phosphate | 305900 | X03674 | VAL394LEU |
| dehydrogenase       | 305900 | X03674 | GLY410ASP |
| Glucose-6-phosphate | 305900 | X03674 | ARG439PRO |
| dehydrogenase       | 305900 | X03674 | ILE35DEL  |
| Glucose-6-phosphate | 305900 | X03674 | GLU317LYS |
| dehydrogenase       | 305900 | X03674 | ILE48THR  |
| Glucose-6-phosphate | 305900 | X03674 | HIS32ARG  |
| dehydrogenase       | 305900 | X03674 | GLY131VAL |

|                                      |        |        |                  |
|--------------------------------------|--------|--------|------------------|
| Glucose-6-phosphate<br>dehydrogenase | 305900 | X03674 | LEU342PHE        |
| Glucose-6-phosphate<br>dehydrogenase | 305900 | X03674 | ALA44GLY         |
| Glucose-6-phosphate<br>dehydrogenase | 305900 | X03674 | PHE173LEU        |
| Glucose-6-phosphate<br>dehydrogenase | 305900 | X03674 | ASP181VAL        |
| Glucose-6-phosphate<br>dehydrogenase | 305900 | X03674 | PRO467ARG        |
| Glucose-6-phosphate<br>dehydrogenase | 305900 | X03674 | ALA361VAL        |
| Glucose-6-phosphate<br>dehydrogenase | 305900 | X03674 | 24-BP DEL, NT953 |
| Glucose-6-phosphate<br>dehydrogenase | 305900 | X03674 | Pro172-->Ser     |
| Glucose-6-phosphate<br>dehydrogenase | 305900 | X03674 | R459L            |
| Glucose-6-phosphate<br>dehydrogenase | 305900 | X03674 | R463H            |
| Glucose-6-phosphate<br>dehydrogenase | 305900 | X03674 | C-->T 563        |
| Glucose-6-phosphate<br>dehydrogenase | 305900 | X03674 | 376A-->G         |
| Glucose-6-phosphate<br>dehydrogenase | 305900 | X03674 | 202G-->A         |
| Glucose-6-phosphate<br>dehydrogenase | 305900 | X03674 | 680G-->T         |
| Glucose-6-phosphate<br>dehydrogenase | 305900 | X03674 | 968T-->C         |
| Glucose-6-phosphate<br>dehydrogenase | 305900 | X03674 | 563C-->T         |

|                                      |        |        |                          |  |
|--------------------------------------|--------|--------|--------------------------|--|
| dehydrogenase                        | 305900 | X03674 | 202G-->A                 |  |
| Glucose-6-phosphate<br>dehydrogenase | 305900 | X03674 | 1311C-->T                |  |
| Glucose-6-phosphate<br>dehydrogenase | 305900 | X03674 | 406 C-->T                |  |
| Glucose-6-phosphate<br>dehydrogenase | 305900 | X03674 | 1155 C-->G               |  |
| Glucose-6-phosphate<br>dehydrogenase | 305900 | X03674 | 185 C-->T, 62 Pro-->Phe  |  |
| Glucose-6-phosphate<br>dehydrogenase | 305900 | X03674 | 695 G-->A                |  |
| Glucose-6-phosphate<br>dehydrogenase | 305900 | X03674 | 1387 C-->T 463 Arg-->Cys |  |
| Glucose-6-phosphate<br>dehydrogenase | 305900 | X03674 | 1246 G-->A               |  |
| Glucose-6-phosphate<br>dehydrogenase | 305900 | X03674 | 1160 G-->A               |  |
| Glucose-6-phosphate<br>dehydrogenase | 305900 | X03674 | Bcl I                    |  |
| Glucose-6-phosphate<br>dehydrogenase | 305900 | X03674 | 202 G-->A                |  |
| Glucose-6-phosphate<br>dehydrogenase | 305900 | X03674 | 335 Ala-->Thr            |  |
| Glucose-6-phosphate<br>dehydrogenase | 305900 | X03674 | G-->T at nt 1376         |  |
| Glucose-6-phosphate<br>dehydrogenase | 305900 | X03674 | G-->A at 1388            |  |
| Glucose-6-phosphate<br>dehydrogenase | 305900 | X03674 | A-->G at nt 95           |  |

|                                      |        |        |                        |
|--------------------------------------|--------|--------|------------------------|
| Glucose-6-phosphate<br>dehydrogenase | 305900 | X03674 | A209G                  |
| Glucose-6-phosphate<br>dehydrogenase | 305900 | X03674 | 493 A-->G              |
| Glucose-6-phosphate<br>dehydrogenase | 305900 | X03674 | 592 C-->T              |
| Glucose-6-phosphate<br>dehydrogenase | 305900 | X03674 | 844 G > C              |
| Glucose-6-phosphate<br>dehydrogenase | 305900 | X03674 | 224 T-->C              |
| Glucose-6-phosphate<br>dehydrogenase | 305900 | X03674 | 488 G-->A              |
| Glucose-6-phosphate<br>dehydrogenase | 305900 | X03674 | 833 C-->T              |
| Glucose-6-phosphate<br>dehydrogenase | 305900 | X03674 | 1360C-->T 454Arg-->Cys |
| Glucose-6-phosphate<br>dehydrogenase | 305900 | X03674 | 383T-->C 128Leu-->Pro  |
| Glucose-6-phosphate<br>dehydrogenase | 305900 | X03674 | 208T-->C 70Tyr-->His   |
| Glucose-6-phosphate<br>dehydrogenase | 305900 | X03674 | 497G-->A 166Arg-->His  |
| Glucose-6-phosphate<br>dehydrogenase | 305900 | X03674 | A-->G 1138 val380iso   |
| Glucose-6-phosphate<br>dehydrogenase | 305900 | X03674 | T-->C 1139 iso380thr   |
| Glucose-6-phosphate<br>dehydrogenase | 305900 | X03674 | C-->G 1177 gly393arg   |
| Glucose-6-phosphate<br>dehydrogenase | 305900 | X03674 | C->T 1187              |
| Glucose-6-phosphate<br>dehydrogenase | 305900 | X03674 | 527A-->G               |

|                        |        |        |                   |       |  |
|------------------------|--------|--------|-------------------|-------|--|
| dehydrogenase          |        |        |                   |       |  |
| Glucose-6-phosphate    | 305900 | X03674 | 1003G-->A         |       |  |
| dehydrogenase          |        |        |                   |       |  |
| Glucose-6-phosphate    | 305900 | X03674 | 1159C-->T         |       |  |
| dehydrogenase          |        |        |                   |       |  |
| Glucose-6-phosphate    | 305900 | X03674 | 1160G-->A         |       |  |
| dehydrogenase          |        |        |                   |       |  |
| Glucose-6-phosphate    | 305900 | X03674 | 1229G-->A         |       |  |
| dehydrogenase          |        |        |                   |       |  |
| Glucose-6-phosphate    | 305900 | X03674 | 1246G-->A         |       |  |
| dehydrogenase          |        |        |                   |       |  |
| Glucose-6-phosphate    | 305900 | X03674 | 1361G-->A         |       |  |
| dehydrogenase          |        |        |                   |       |  |
| Glucose-6-phosphate    | 305900 | X03674 | C-->T 563         |       |  |
| dehydrogenase          |        |        |                   |       |  |
| Glucose-6-phosphate    | 305900 | X03674 | C-->T 1311        |       |  |
| dehydrogenase          |        |        |                   |       |  |
| Glucose-6-phosphate    | 305900 | X03674 | 241 C to T        |       |  |
| dehydrogenase          |        |        |                   |       |  |
| Glucose-6-phosphate    | 305900 | X03674 | 487 G-->A         |       |  |
| dehydrogenase          |        |        |                   |       |  |
| glutathione peroxidase | 138320 | Y00433 |                   | P197L |  |
| GPx1                   |        |        |                   |       |  |
| glutathione peroxidase | 138320 | Y00433 | 1167T/C Silent    |       |  |
| GPx1                   |        |        |                   |       |  |
| glutathione peroxidase | 138319 | X68314 | A/T intron        |       |  |
| GPx2                   |        |        |                   |       |  |
| glutathione peroxidase | 138319 | X68314 | TC repeats intron |       |  |
| GPx2                   |        |        |                   |       |  |
| glutathione peroxidase | 138321 | X58295 | none found        |       |  |
| GPx3                   |        |        |                   |       |  |



|                                                       |        |               |                       |
|-------------------------------------------------------|--------|---------------|-----------------------|
| glutathione peroxidase<br>GPx4                        | 138322 | X71973        | none found            |
| glutathione peroxidase<br>GPx5                        | 603435 | AJ005277      | none found            |
| Glutathione-S-<br>transferase 1/MGST1<br>(microsomal) | 138330 | AH003674      | none found            |
| Glutathione-S-<br>transferase 2/MGST2<br>(microsomal) | 601733 | NM_00241<br>3 | none found            |
| Glutathione-S-<br>transferase 6                       | 138391 | *****         | none found            |
| glutathione-S-<br>transferase GSTM3                   | 138390 | J05459        | 3bp deletion intron 6 |
| glutathione-S-<br>transferase GSTT1                   | 600436 | X79389        | null genotype         |
| glutathione-S-<br>transferase GSTT2                   | 600437 | L38503        | none found            |
| Glutathione-S-<br>transferase, alpha<br>1/GSTA1       | 138359 | L13269        | none found            |
| Glutathione-S-<br>transferase, alpha<br>2/GSTA2       | 138360 | M15872        | none found            |
| Glutathione-S-<br>transferase, kappa<br>1/GSTK1       | 602321 | *****         | none found            |
| Glutathione-S-<br>transferase, mu 1-<br>like/GSTM1L   | 138270 | *****         | none found            |
| Glutathione-S-                                        | 138350 | J03817        | gene deletion         |

|                                                           |        |           |                              |  |
|-----------------------------------------------------------|--------|-----------|------------------------------|--|
| transferase, mu<br>1/GSTM1                                | 138380 | NM_000848 | none found                   |  |
| Glutathione-S-<br>transferase, mu<br>2/GSTM2 (muscle)     | 138333 | NM_000850 | none found                   |  |
| Glutathione-S-<br>transferase, mu<br>4/GSTM4              | 138385 | NM_000851 | none found                   |  |
| Glutathione-S-<br>transferase, mu<br>5/GSTM5 (brain/lung) | 134660 | NM_000852 | ILE104VAL                    |  |
| Glutathione-S-<br>transferase, pi/GSTP1                   | 134660 | NM_000852 | ALA113VAL                    |  |
| Glutathione-S-<br>transferase, pi/GSTP1                   | 134660 | NM_000852 | BamHI                        |  |
| Glutathione-S-<br>transferase, pi/GSTP1                   | 134660 | NM_000852 | (ATAAA)n<br>upstream of gene |  |
| Glutathione-S-<br>transferase, pi/GSTP1                   | 138610 |           | none found                   |  |
| GLYCOPROTEIN,<br>ALPHA-I-ACID, OF<br>SERUM, TYPE 2        | 602403 | X92106    | ILE443VAL                    |  |
| H.sapiens mRNA for<br>bleomycin hydrolase                 | 164012 | X61498    |                              |  |
| H.sapiens mRNA for<br>NF-kB subunit                       |        |           | A939G                        |  |
| histamine N-<br>methyltransferase                         |        |           | Thr105Ile                    |  |
| histamine N-<br>methyltransferase                         |        |           |                              |  |
| Homo sapiens ABC                                          | MOATB  | AF071202  | none found                   |  |

|                                                                                                |        |          |               |
|------------------------------------------------------------------------------------------------|--------|----------|---------------|
| transporter MOAT-B<br>(MOAT-B) mRNA,<br>complete cds                                           | 103730 | M12272   | ile349-to-val |
| Homo sapiens alcohol<br>dehydrogenase class I<br>gamma subunit<br>(ADH3) mRNA,<br>complete cds | 103730 | M12272   | ARG271GLU     |
| Homo sapiens gamma-<br>glutamylcysteine<br>synthetase light subunit<br>mRNA, complete cds      | 601176 | L35546   | none found    |
| Homo sapiens mRNA<br>for 25-hydroxyvitamin<br>D3 1-alpha-<br>hydroxylase, complete<br>cds      | 264700 | AB005038 | ARG107HIS     |
| Homo sapiens mRNA<br>for 25-hydroxyvitamin<br>D3 1-alpha-<br>hydroxylase, complete<br>cds      | 264700 | AB005038 | GLY125GLU     |
| Homo sapiens mRNA<br>for 25-hydroxyvitamin<br>D3 1-alpha-<br>hydroxylase, complete<br>cds      | 264700 | AB005038 | ARG335PRO     |

|                                                                                           |        |          |                     |
|-------------------------------------------------------------------------------------------|--------|----------|---------------------|
| cds<br>Homo sapiens mRNA<br>for 25-hydroxyvitamin<br>D3 1-alpha-<br>hydroxylase, complete | 264700 | AB005038 | PRO382SER           |
| cds<br>Homo sapiens mRNA<br>for 25-hydroxyvitamin<br>D3 1-alpha-<br>hydroxylase, complete | 264700 | AB005038 | 1-BP DEL frameshift |
| cds<br>Homo sapiens mRNA<br>for 25-hydroxyvitamin<br>D3 1-alpha-<br>hydroxylase, complete | 264700 | AB005038 | 1-BP DEL, 958G      |
| cds<br>Homo sapiens mRNA<br>for 25-hydroxyvitamin<br>D3 1-alpha-<br>hydroxylase, complete | 264700 | AB005038 | 7-BP DUP            |
| cds<br>Homo sapiens mRNA<br>for carbonyl reductase<br>3, complete cds                     | 603608 | AB004854 | none found          |
| Homo sapiens<br>paraoxonase 2 (PON2)<br>mRNA, complete cds                                | 602447 | L48513   | CYS311SER           |
| Homo sapiens<br>paraoxonase 2 (PON2)<br>mRNA, complete cds                                | 602447 | L48513   | ALA148GLY           |
| Homo sapiens                                                                              | 602720 | L48516   | none found          |

|                                                                  |        |          |            |
|------------------------------------------------------------------|--------|----------|------------|
| paraoxonase 3 (PON3)<br>mRNA, 3' end of cds                      | 602239 | AF005418 | none found |
| Homo sapiens retinoic<br>acid hydroxylase<br>mRNA, complete cds  | SMRP   | AB005659 | none found |
| Homo sapiens SMRP<br>mRNA, complete cds                          | 600086 | U07821   | none found |
| Human alcohol<br>dehydrogenase<br>(ADH7) mRNA,<br>complete cds   | 103735 | M68895   | none found |
| Human alcohol<br>dehydrogenase 6 gene,<br>complete cds           | 103710 | M29872   | MspI       |
| Human aldehyde<br>dehydrogenase<br>(ALDH8) mRNA,<br>complete cds | 601917 | U37519   | none found |
| Human aldehyde<br>dehydrogenase 6<br>mRNA, complete cds          | 600463 | U07919   | none found |
| Human aldehyde<br>dehydrogenase ALDH7<br>mRNA, complete cds      | 600466 | U10868   | none found |
| Human aldehyde<br>dehydrogenase type III<br>(ALDHIII) mRNA,      | 100660 | M74542   | none found |

|                                                                                       |        |        |            |
|---------------------------------------------------------------------------------------|--------|--------|------------|
| complete cds                                                                          | 138600 | M13692 | VAL156MET  |
| Human alpha-1 acid<br>glycoprotein mRNA,<br>complete cds                              | 138600 | M13692 | GLN20ARG   |
| Human alpha-1 acid<br>glycoprotein mRNA,<br>complete cds                              | 151530 | M22324 | none found |
| Human aminopeptidase<br>N/CD13 mRNA<br>encoding<br>aminopeptidase N,<br>complete cds  | 600338 | L32179 | none found |
| Human arylacetamide<br>deacetylase mRNA,<br>complete cds                              | 114830 | J04056 | none found |
| Human carbonyl<br>reductase mRNA,<br>complete cds                                     | 103720 | M24317 | ARG47HIS   |
| Human class I alcohol<br>dehydrogenase<br>(ADH2) beta-1 subunit<br>mRNA, complete cds | 103720 | M24317 | ARG369CYS  |
| Human class I alcohol<br>dehydrogenase<br>(ADH2) beta-1 subunit<br>mRNA, complete cds | 103740 | M15943 | -75A-->C   |
| Human class II<br>alcohol<br>dehydrogenase<br>(ADH4) pi subunit<br>mRNA, complete cds |        |        |            |

|                                                                        |        |        |                                |           |
|------------------------------------------------------------------------|--------|--------|--------------------------------|-----------|
| Human factor KBF1<br>mRNA, complete cds                                | 164011 | M55643 | (CA)n                          |           |
| Human fatty aldehyde<br>dehydrogenase<br>(FALDH) mRNA,<br>complete cds | 270200 | L47162 | 1-BP DEL, 525T                 |           |
| Human fatty aldehyde<br>dehydrogenase<br>(FALDH) mRNA,<br>complete cds | 270200 | L47162 | 1-BP DEL, 808G                 |           |
| Human fatty aldehyde<br>dehydrogenase<br>(FALDH) mRNA,<br>complete cds | 270200 | L47162 | 3-BP DEL/21-BP<br>INS          |           |
| Human fatty aldehyde<br>dehydrogenase<br>(FALDH) mRNA,<br>complete cds | 270200 | L47162 |                                | ALA314GLY |
| Human fatty aldehyde<br>dehydrogenase<br>(FALDH) mRNA,<br>complete cds | 270200 | L47162 |                                | PRO315ALA |
| Human fatty aldehyde<br>dehydrogenase<br>(FALDH) mRNA,<br>complete cds | 270200 | L47162 |                                | CYS214TYR |
| Human fatty aldehyde<br>dehydrogenase<br>(FALDH) mRNA,<br>complete cds | 270200 | L47162 |                                | PRO315SER |
| Human fatty aldehyde<br>dehydrogenase<br>(FALDH) mRNA,<br>complete cds | 270200 | L47162 | 2-BP DEL, 1297GA<br>frameshift |           |

|                                                                                                |        |        |                               |           |
|------------------------------------------------------------------------------------------------|--------|--------|-------------------------------|-----------|
| dehydrogenase<br>(FALDH) mRNA,<br>complete cds                                                 | 270200 | L47162 | 5-BP INS, NT1311              |           |
| Human fatty aldehyde<br>dehydrogenase<br>(FALDH) mRNA,<br>complete cds                         | 602733 | U34252 |                               | CYS115SER |
| Human gamma-<br>aminobutyraldehyde<br>dehydrogenase mRNA,<br>complete cds                      | 230450 | M90656 | A-->T 1109 His370Leu          |           |
| Human gamma-<br>glutamylcysteine<br>synthetase (GCS)<br>mRNA, complete cds                     | 230450 | M90656 | (CAGC) <sub>n</sub> 1972-1975 |           |
| Human gamma-<br>glutamylcysteine<br>synthetase (GCS)<br>mRNA, complete cds                     | 137168 | M64099 | none found                    |           |
| Human gamma-<br>glutnyl transpeptidase-<br>related protein (GGT-<br>Rel) mRNA, complete<br>cds | 601002 | U34683 |                               | ARG164GLN |
| Human glutathione<br>synthetase mRNA,<br>complete cds                                          | 601002 | U34683 | 1-BP DEL frameshift           |           |
| Human glutathione<br>synthetase mRNA,<br>complete cds                                          | 601002 | U34683 |                               | ARG267TRP |



|                                                       |        |        |                      |
|-------------------------------------------------------|--------|--------|----------------------|
| synthetase mRNA,<br>complete cds                      | 601002 | U34683 | ARG283CYS            |
| Human glutathione<br>synthetase mRNA,<br>complete cds | 601002 | U34683 | ARG125CYS            |
| Human glutathione<br>synthetase mRNA,<br>complete cds | 601002 | U34683 | PRO314LEU            |
| Human glutathione<br>synthetase mRNA,<br>complete cds | 601002 | U34683 | 6-BP DEL VAL-GLN del |
| Human glutathione<br>synthetase mRNA,<br>complete cds | 601002 | U34683 | ASP219GLY            |
| Human kidney mRNA<br>for catalase                     | 115500 | X04076 | IVS4, G-A, +5        |
| Human kidney mRNA<br>for catalase                     | 115500 | X04076 | A to T -21           |
| Human kidney mRNA<br>for catalase                     | 115500 | X04076 | C to A -20           |
| Human kidney mRNA<br>for catalase                     | 115500 | X04076 | C to T -18           |
| Human kidney mRNA<br>for catalase                     | 115500 | X04076 | T to C 4             |
| Human kidney mRNA<br>for catalase                     | 115500 | X04076 | T to C 44            |
| Human kidney mRNA<br>for catalase                     | 115500 | X04076 | T to C 49            |

|                                                   |        |        |             |
|---------------------------------------------------|--------|--------|-------------|
| Human kidney mRNA<br>for catalase                 | 115500 | X04076 | C to T 12   |
| Human kidney mRNA<br>for catalase                 | 115500 | X04076 | C to A 27   |
| Human kidney mRNA<br>for catalase                 | 115500 | X04076 | 358 T-->del |
| Human kidney mRNA<br>for catalase                 | 115500 | X04076 | MspI        |
| Human messenger<br>RNA for serum<br>albumin (HSA) | 103600 | V00494 | ARG-2HIS    |
| Human messenger<br>RNA for serum<br>albumin (HSA) | 103600 | V00494 | ARG-1GLN    |
| Human messenger<br>RNA for serum<br>albumin (HSA) | 103600 | V00494 | ARG-1PRO    |
| Human messenger<br>RNA for serum<br>albumin (HSA) | 103600 | V00494 | ASP1VAL     |
| Human messenger<br>RNA for serum<br>albumin (HSA) | 103600 | V00494 | HIS3GLN     |
| Human messenger<br>RNA for serum<br>albumin (HSA) | 103600 | V00494 | ARG114GLY   |
| Human messenger<br>RNA for serum<br>albumin (HSA) | 103600 | V00494 | GLU119LYS   |
| Human messenger<br>RNA for serum<br>albumin (HSA) | 103600 | V00494 | ASP269GLY   |

|                                                   |        |        |           |
|---------------------------------------------------|--------|--------|-----------|
| albumin (HSA)                                     | 103600 | V00494 | LYS313ASN |
| Human messenger<br>RNA for serum<br>albumin (HSA) |        |        |           |
| Human messenger<br>RNA for serum<br>albumin (HSA) | 103600 | V00494 | ALA320THR |
| Human messenger<br>RNA for serum<br>albumin (HSA) |        |        |           |
| Human messenger<br>RNA for serum<br>albumin (HSA) | 103600 | V00494 | ARG-2CYS  |
| Human messenger<br>RNA for serum<br>albumin (HSA) |        |        |           |
| Human messenger<br>RNA for serum<br>albumin (HSA) | 103600 | V00494 | GLU321LYS |
| Human messenger<br>RNA for serum<br>albumin (HSA) |        |        |           |
| Human messenger<br>RNA for serum<br>albumin (HSA) | 103600 | V00494 | GLU354LYS |
| Human messenger<br>RNA for serum<br>albumin (HSA) |        |        |           |
| Human messenger<br>RNA for serum<br>albumin (HSA) | 103600 | V00494 | GLU358LYS |
| Human messenger<br>RNA for serum<br>albumin (HSA) |        |        |           |
| Human messenger<br>RNA for serum<br>albumin (HSA) | 103600 | V00494 | ASP365HIS |
| Human messenger<br>RNA for serum<br>albumin (HSA) |        |        |           |
| Human messenger<br>RNA for serum<br>albumin (HSA) | 103600 | V00494 | LYS372GLU |
| Human messenger<br>RNA for serum<br>albumin (HSA) |        |        |           |
| Human messenger<br>RNA for serum<br>albumin (HSA) | 103600 | V00494 | ASP375ASN |
| Human messenger<br>RNA for serum<br>albumin (HSA) |        |        |           |
| Human messenger<br>RNA for serum<br>albumin (HSA) | 103600 | V00494 | GLU376LYS |
| Human messenger<br>RNA for serum<br>albumin (HSA) |        |        |           |

|                                                   |        |        |               |
|---------------------------------------------------|--------|--------|---------------|
| Human messenger<br>RNA for serum<br>albumin (HSA) | 103600 | V00494 | GLU382LYS     |
| Human messenger<br>RNA for serum<br>albumin (HSA) | 103600 | V00494 | GLU501LYS     |
| Human messenger<br>RNA for serum<br>albumin (HSA) | 103600 | V00494 | LYS541GLU     |
| Human messenger<br>RNA for serum<br>albumin (HSA) | 103600 | V00494 | ASP550GLY     |
| Human messenger<br>RNA for serum<br>albumin (HSA) | 103600 | V00494 | ASP563ASN     |
| Human messenger<br>RNA for serum<br>albumin (HSA) | 103600 | V00494 | GLU565LYS     |
| Human messenger<br>RNA for serum<br>albumin (HSA) | 103600 | V00494 | GLU570LYS     |
| Human messenger<br>RNA for serum<br>albumin (HSA) | 103600 | V00494 | LYS573GLU     |
| Human messenger<br>RNA for serum<br>albumin (HSA) | 103600 | V00494 | LYS574ASN     |
| Human messenger<br>RNA for serum<br>albumin (HSA) | 103600 | V00494 | IVS6, A-G, -2 |
| Human messenger<br>RNA for serum<br>albumin (HSA) | 103600 | V00494 | EX14DEL       |

|                                             |        |        |                  |
|---------------------------------------------|--------|--------|------------------|
| RNA for serum albumin (HSA)                 | 103600 | V00494 | LYS536GLU        |
| Human messenger RNA for serum albumin (HSA) | 103600 | V00494 | ARG-2CYS         |
| Human messenger RNA for serum albumin (HSA) | 103600 | V00494 | ARG-1LEU         |
| Human messenger RNA for serum albumin (HSA) | 103600 | V00494 | GLN580LYS        |
| Human messenger RNA for serum albumin (HSA) | 103600 | V00494 | GLU60LYS         |
| Human messenger RNA for serum albumin (HSA) | 103600 | V00494 | GLU82LYS         |
| Human messenger RNA for serum albumin (HSA) | 103600 | V00494 | ASP494ASN        |
| Human messenger RNA for serum albumin (HSA) | 103600 | V00494 | ASP365VAL        |
| Human messenger RNA for serum albumin (HSA) | 103600 | V00494 | HIS128ARG        |
| Human messenger RNA for serum albumin (HSA) | 103600 | V00494 | IVS13DS, G-C, +1 |

|                                                                    |        |        |                       |
|--------------------------------------------------------------------|--------|--------|-----------------------|
| albumin (HSA)<br>Human messenger<br>RNA for serum<br>albumin (HSA) | 103600 | V00494 | LYS240GLU             |
| Human messenger<br>RNA for serum<br>albumin (HSA)                  | 103600 | V00494 | AAT267AAAT frameshift |
| Human messenger<br>RNA for serum<br>albumin (HSA)                  | 103600 | V00494 | ARG218HIS             |
| Human messenger<br>RNA for serum<br>albumin (HSA)                  | 103600 | V00494 | HIS3TYR               |
| Human messenger<br>RNA for serum<br>albumin (HSA)                  | 103600 | V00494 | LYS225GLN             |
| Human messenger<br>RNA for serum<br>albumin (HSA)                  | 103600 | V00494 | LYS276ASN             |
| Human messenger<br>RNA for serum<br>albumin (HSA)                  | 103600 | V00494 | TGC567GC frameshift   |
| Human messenger<br>RNA for serum<br>albumin (HSA)                  | 103600 | V00494 | TYR140CYS             |
| Human messenger<br>RNA for serum<br>albumin (HSA)                  | 103600 | V00494 | ASP63ASN              |
| Human messenger<br>RNA for serum<br>albumin (HSA)                  | 103600 | V00494 | CYS177PHE             |

|                                                   |        |        |                 |
|---------------------------------------------------|--------|--------|-----------------|
| Human messenger<br>RNA for serum<br>albumin (HSA) | 103600 | V00494 | GLN268ARG       |
| Human messenger<br>RNA for serum<br>albumin (HSA) | 103600 | V00494 | ASN318LYS       |
| Human messenger<br>RNA for serum<br>albumin (HSA) | 103600 | V00494 | GLU333LYS       |
| Human messenger<br>RNA for serum<br>albumin (HSA) | 103600 | V00494 | GLU376ASN       |
| Human messenger<br>RNA for serum<br>albumin (HSA) | 103600 | V00494 | GLU479LYS       |
| Human messenger<br>RNA for serum<br>albumin (HSA) | 103600 | V00494 | GLU505LYS       |
| Human messenger<br>RNA for serum<br>albumin (HSA) | 103600 | V00494 | ARG218PRO       |
| Human messenger<br>RNA for serum<br>albumin (HSA) | 103600 | V00494 | LEU66PRO        |
| Human messenger<br>RNA for serum<br>albumin (HSA) | 103600 | V00494 | Arg218His       |
| Human messenger<br>RNA for serum<br>albumin (HSA) | 103600 | V00494 | HaeIII intron 7 |
| Human mitochondrial                               | 600125 | L13286 | none found      |

|                                                                                                                                       |        |        |                       |           |
|---------------------------------------------------------------------------------------------------------------------------------------|--------|--------|-----------------------|-----------|
| 1,25-dihydroxyvitamin<br>D3 24-hydroxylase<br>mRNA, complete cds<br>Human mRNA for<br>brain pyruvate<br>dehydrogenase (EC<br>1.2.4.1) | 312170 | X52709 | 4-BP DEL              |           |
| Human mRNA for<br>brain pyruvate<br>dehydrogenase (EC<br>1.2.4.1)                                                                     | 312170 | X52709 | 7-BP DEL              |           |
| Human mRNA for<br>brain pyruvate<br>dehydrogenase (EC<br>1.2.4.1)                                                                     | 312170 | X52709 |                       | ARG378HIS |
| Human mRNA for<br>brain pyruvate<br>dehydrogenase (EC<br>1.2.4.1)                                                                     | 312170 | X52709 |                       | LYS313DEL |
| Human mRNA for<br>brain pyruvate<br>dehydrogenase (EC<br>1.2.4.1)                                                                     | 312170 | X52709 | 2-BP DEL frameshift   |           |
| Human mRNA for<br>brain pyruvate<br>dehydrogenase (EC<br>1.2.4.1)                                                                     | 312170 | X52709 | 20-BP DEL,<br>EX11DEL |           |
| Human mRNA for<br>brain pyruvate<br>dehydrogenase (EC<br>1.2.4.1)                                                                     | 312170 | X52709 | 21-BP INS             |           |



|                                                                   |        |        |                     |
|-------------------------------------------------------------------|--------|--------|---------------------|
| Human mRNA for<br>brain pyruvate<br>dehydrogenase (EC<br>1.2.4.1) | 312170 | X52709 | ARG234GLY           |
| Human mRNA for<br>brain pyruvate<br>dehydrogenase (EC<br>1.2.4.1) | 312170 | X52709 | ARG302CYS           |
| Human mRNA for<br>brain pyruvate<br>dehydrogenase (EC<br>1.2.4.1) | 312170 | X52709 | 4-BP INS frameshift |
| Human mRNA for<br>brain pyruvate<br>dehydrogenase (EC<br>1.2.4.1) | 312170 | X52709 | ASP258ALA           |
| Human mRNA for<br>brain pyruvate<br>dehydrogenase (EC<br>1.2.4.1) | 312170 | X52709 | PHE205LEU           |
| Human mRNA for<br>brain pyruvate<br>dehydrogenase (EC<br>1.2.4.1) | 312170 | X52709 | TYR243ASN           |
| Human mRNA for<br>brain pyruvate<br>dehydrogenase (EC<br>1.2.4.1) | 312170 | X52709 | ASP315ASN           |
| Human mRNA for<br>brain pyruvate<br>dehydrogenase (EC<br>1.2.4.1) | 312170 | X52709 | MET282LEU           |

|                                                                               |        |        |                  |
|-------------------------------------------------------------------------------|--------|--------|------------------|
| 1.2.4.1)<br>Human mRNA for<br>brain pyruvate<br>dehydrogenase (EC<br>1.2.4.1) | 312170 | X52709 | -BP INS FS141TER |
| Human mRNA for<br>brain pyruvate<br>dehydrogenase (EC<br>1.2.4.1)             | 312170 | X52709 | ARG10PRO         |
| Human mRNA for<br>brain pyruvate<br>dehydrogenase (EC<br>1.2.4.1)             | 312170 | X52709 | 13-BP INS, EX10  |
| Human mRNA for<br>brain pyruvate<br>dehydrogenase (EC<br>1.2.4.1)             | 312170 | X52709 | 36-BP INS        |
| Human mRNA for<br>dipeptidase                                                 | 179780 | D13138 | none found       |
| Human mRNA for<br>glutathione reductase<br>(EC 1.6.4.2)                       | 138300 | X15722 | none found       |
| Human mRNA for<br>pancreatic gamma-<br>glutamyltransferase                    | 231950 | X60069 | none found       |
| Human multidrug<br>resistance-associated<br>protein homolog<br>(MRP3)         | CMOAT2 | U83659 | none found       |
| Human<br>Na/taurocholate                                                      | 182396 | L21893 | none found       |

| cotransporting<br>polypeptide mRNA,<br>complete cds |        | 23-bp VNTR |                                                                |
|-----------------------------------------------------|--------|------------|----------------------------------------------------------------|
| Monoamine Oxidase<br>A; MAOA                        | 309850 | M69226     | 3rd base of codon 941<br>941 G>T                               |
| Monoamine Oxidase<br>A; MAOA                        | 309850 | M69226     | A1026T ProlineProline                                          |
| Monoamine Oxidase<br>A; MAOA                        | 309850 | M69226     | A1559G LysineArginine                                          |
| Monoamine Oxidase<br>A; MAOA                        | 309850 | M69226     | A385C ArginineArginine<br>e                                    |
| Monoamine Oxidase<br>A; MAOA                        | 309850 | M69226     | C1410T Aspartic<br>AcidAspartic<br>Acid                        |
| Monoamine Oxidase<br>A; MAOA                        | 309850 | M69226     | C886T GlutamineTermin<br>ation codon                           |
| Monoamine Oxidase<br>A; MAOA                        | 309850 | M69226     | C886T Glutamine296T<br>ermination<br>codon                     |
| Monoamine Oxidase<br>A; MAOA                        | 309850 | M69226     | exon 14 -- RFLP<br>(EcoRV enzyme)<br>length of (CA)n<br>repeat |
| Monoamine Oxidase<br>A; MAOA                        | 309850 | M69226     | RFLP (EcoRV<br>enzyme)                                         |
| Monoamine Oxidase<br>A; MAOA                        | 309850 | M69226     | RFLP (Pst I)                                                   |
| Monoamine Oxidase<br>A; MAOA                        | 309850 | M69226     | T891G                                                          |

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|                                                                  |        |        |                                                         |
|------------------------------------------------------------------|--------|--------|---------------------------------------------------------|
| Monoamine Oxidase<br>A; MAOA                                     | 309850 | M69226 | T891G Arginine                                          |
| Monoamine Oxidase<br>B; MAOB                                     | 309860 | M69177 | e<br>(GT)n repeat                                       |
| Monoamine Oxidase<br>B; MAOB                                     | 309860 | M69177 | 36 bases upstream<br>from intron 13-exon<br>14 boundary |
| Monoamine Oxidase<br>B; MAOB                                     | 309860 | M69177 | A at position 644 of<br>intron 13                       |
| Monoamine Oxidase<br>B; MAOB                                     | 309860 | M69177 | G at position 644 of<br>intron 13                       |
| Multidrug resistance<br>associated protein<br>MRP1               | 158343 | L05628 | RFLP (MaeIII<br>enzyme)<br>none found                   |
| Multidrug resistance<br>associated protein<br>MRP2               | 601107 | U83659 | none found                                              |
| Multidrug resistance<br>protein MDR1                             | 171050 | X96395 | HindIII                                                 |
| Multidrug resistance<br>protein MDR1                             | 171050 | X96395 | Ser893Ala                                               |
| Multidrug resistance<br>protein MDR1                             | 171050 | X96395 | GLY185VAL                                               |
| Multidrug resistance<br>protein MDR3/P-<br>glycoprotein 3/P-gly3 | 602347 | X06181 | none found                                              |
| Myeloperoxidase/MPO                                              | 254600 |        | ARG569TRP                                               |
| Myeloperoxidase/MPO                                              | 254600 |        | TYR173CYS                                               |
| Myeloperoxidase/MPO                                              | 254600 |        | MET251THR                                               |

|                                                        |        |                                                |
|--------------------------------------------------------|--------|------------------------------------------------|
| myeloperoxidase/MPO                                    | 254600 | G to A in the promoter<br>-463 G/A             |
| myeloperoxidase/MPO                                    | 254600 | Dinucleotide repeat                            |
| myeloperoxidase/MPO                                    | 254600 | EcoRV RFLP                                     |
| myeloperoxidase/MPO                                    | 254600 | PstI.                                          |
| N-acetyltransferase<br>1/arylamine acetylase<br>1/NAT1 | 108345 | NM_000662<br>POLYADENYLATION SIGNAL<br>VARIANT |
| N-acetyltransferase<br>1/arylamine acetylase<br>1/NAT1 | 108345 | NM_000662<br>VAL149ILE                         |
| N-acetyltransferase<br>1/arylamine acetylase<br>1/NAT1 | 108345 | NM_000662<br>C1095A                            |
| N-acetyltransferase<br>1/arylamine acetylase<br>1/NAT1 | 108345 | NM_000662<br>T1088A                            |
| N-acetyltransferase<br>1/arylamine acetylase<br>1/NAT1 | 108345 | NM_000662<br>C1095A                            |
| N-acetyltransferase<br>1/arylamine acetylase<br>1/NAT1 | 108345 | NM_000662<br>9 bp deletion                     |
| N-acetyltransferase<br>1/arylamine acetylase<br>1/NAT1 | 108345 | NM_000662<br>G560A                             |
| N-acetyltransferase<br>1/arylamine acetylase<br>1/NAT1 | 108345 | NM_000662<br>C559T                             |
| N-acetyltransferase<br>1/arylamine acetylase<br>1/NAT1 | 108345 | NM_000662<br>C190T                             |

|                                                        |        |               |                      |  |
|--------------------------------------------------------|--------|---------------|----------------------|--|
| 1/arylamide acetylase<br>1/NAT1                        | 2      |               |                      |  |
| N-acetyltransferase<br>1/arylamide acetylase<br>1/NAT1 | 108345 | NM_00066<br>2 | 350-351 (GG to CC)   |  |
| N-acetyltransferase<br>1/arylamide acetylase<br>1/NAT1 | 108345 | NM_00066<br>2 | 497-499 (GGG to CCC) |  |
| N-acetyltransferase<br>1/arylamide acetylase<br>1/NAT1 | 108345 | NM_00066<br>2 | C97T                 |  |
| N-acetyltransferase<br>1/arylamide acetylase<br>1/NAT1 | 108345 | NM_00066<br>2 | C190T                |  |
| N-acetyltransferase<br>1/arylamide acetylase<br>1/NAT1 | 108345 | NM_00066<br>2 | T402C                |  |
| N-acetyltransferase<br>1/arylamide acetylase<br>1/NAT1 | 108345 | NM_00066<br>2 | G445A                |  |
| N-acetyltransferase<br>1/arylamide acetylase<br>1/NAT1 | 108345 | NM_00066<br>2 | G459A                |  |
| N-acetyltransferase<br>1/arylamide acetylase<br>1/NAT1 | 108345 | NM_00066<br>2 | T640G                |  |
| N-acetyltransferase<br>1/arylamide acetylase<br>1/NAT1 | 108345 | NM_00066<br>2 | C559T                |  |
| N-acetyltransferase<br>1/arylamide acetylase<br>1/NAT1 | 108345 | NM_00066<br>2 | G560A                |  |

|                                              |        |           |       |                           |
|----------------------------------------------|--------|-----------|-------|---------------------------|
| 1/NAT1                                       | 108345 | NM_000662 | A613G |                           |
| N-acetyltransferase<br>1/arylamide acetylase |        |           |       |                           |
| 1/NAT1                                       | 108345 | NM_000662 | A752T |                           |
| N-acetyltransferase<br>1/arylamide acetylase |        |           |       |                           |
| 1/NAT1                                       | 108345 | NM_000662 | T777C |                           |
| N-acetyltransferase<br>1/arylamide acetylase |        |           |       |                           |
| 1/NAT1                                       | 108345 | NM_000662 | G781A |                           |
| N-acetyltransferase<br>1/arylamide acetylase |        |           |       |                           |
| 1/NAT1                                       | 108345 | NM_000662 | A787G |                           |
| N-acetyltransferase<br>1/arylamide acetylase |        |           |       |                           |
| 1/NAT1                                       | 108345 | NM_000662 |       | Arg187 to a<br>stop codon |
| N-acetyltransferase<br>1/arylamide acetylase |        |           |       |                           |
| 1/NAT1                                       | 108345 | NM_000662 |       | Arg187 to Gln             |
| N-acetyltransferase<br>1/arylamide acetylase |        |           |       |                           |
| 1/NAT1                                       | 108345 | NM_000662 |       |                           |
| N-acetyltransferase<br>1/arylamide acetylase |        |           |       |                           |
| 1/NAT1                                       | 108345 | NM_000662 |       | -344 (C-->T)              |
| N-acetyltransferase<br>1/arylamide acetylase |        |           |       |                           |
| 1/NAT1                                       | 108345 | NM_000662 |       | 640 T-->G Ser-->Ala       |
| N-acetyltransferase<br>1/arylamide acetylase |        |           |       |                           |
| 1/NAT1                                       | 243400 | NM_000015 |       | ARG197GLN                 |
| N-acetyltransferase<br>2/arylamide acetylase |        |           |       |                           |
| 2/NAT2                                       |        |           |       |                           |

|                                                        |        |               |                        |
|--------------------------------------------------------|--------|---------------|------------------------|
| N-acetyltransferase<br>2/arylamine acetylase<br>2/NAT2 | 243400 | NM_00001<br>5 | ILE114THR              |
| N-acetyltransferase<br>2/arylamine acetylase<br>2/NAT2 | 243400 | NM_00001<br>5 | LYS268ARG              |
| N-acetyltransferase<br>2/arylamine acetylase<br>2/NAT2 | 243400 | NM_00001<br>5 | 857G-A GLY-GLU         |
| N-acetyltransferase<br>2/arylamine acetylase<br>2/NAT2 | 243400 | NM_00001<br>5 | 191G-A Arg64-->Gln     |
| N-acetyltransferase<br>2/arylamine acetylase<br>2/NAT2 | 243400 | NM_00001<br>5 | C282T (silent)         |
| N-acetyltransferase<br>2/arylamine acetylase<br>2/NAT2 | 243400 | NM_00001<br>5 | T341C Ile114-->Thr     |
| N-acetyltransferase<br>2/arylamine acetylase<br>2/NAT2 | 243400 | NM_00001<br>5 | 481C-->T silent        |
| N-acetyltransferase<br>2/arylamine acetylase<br>2/NAT2 | 243400 | NM_00001<br>5 | 590 G-->A Arg197-->Gln |
| N-acetyltransferase<br>2/arylamine acetylase<br>2/NAT2 | 243400 | NM_00001<br>5 | 803 A-->G Lys268-->Arg |
| N-acetyltransferase<br>2/arylamine acetylase<br>2/NAT2 | 243400 | NM_00001<br>5 | 857 G-->A Gly286-->Glu |
| N-acetyltransferase                                    | 243400 | NM_00001      | C759T                  |



|                                                                                        |        |           |                               |           |
|----------------------------------------------------------------------------------------|--------|-----------|-------------------------------|-----------|
| 2/arylamide acetylase<br>2/NAT2                                                        | 5      |           |                               |           |
| NAD(P)H menadiene<br>oxidoreductase 1,<br>dioxin-<br>inducible/NMOR1/diaphorase 4/DIA4 | 125860 | NM_000903 | 609C>T                        | pro187ser |
| NAD(P)H menadiene<br>oxidoreductase 2,<br>dioxin-<br>inducible/NMOR2                   | 160998 | NM_000904 | none found                    |           |
| NEUROPATHY<br>TARGET ESTERASE                                                          | 603197 |           | none found                    |           |
| nicotinamide N-<br>methyltransferase/NNMT                                              | 600008 | NM_006169 | eight SNPs within<br>intron 1 |           |
| O6 alkylguanine-DNA<br>alkyltransferase                                                | 156569 | M60761    | GGA to AGA                    | gly160arg |
| O6 alkylguanine-DNA<br>alkyltransferase                                                | 156569 | M60761    | 1034A>G                       |           |
| O6 alkylguanine-DNA<br>alkyltransferase                                                | 156569 | M60761    | 1099C>T                       |           |
| O6 alkylguanine-DNA<br>alkyltransferase                                                | 156569 | M60761    | 79G>T                         |           |
| paraoxonase 1/PON1<br>(arylesterase)                                                   | 168820 | AH004193  |                               | GLN192ARG |
| paraoxonase 1/PON1<br>(arylesterase)                                                   | 168820 | AH004193  |                               | MET54LEU  |
| paraoxonase 1/PON1<br>(arylesterase)                                                   | 168820 | AH004193  |                               | Leu55Met  |
| paraoxonase 1/PON1                                                                     | 168820 | AH004193  | CA repeat                     | intron 4. |

|                         |        |                       |                           |
|-------------------------|--------|-----------------------|---------------------------|
| (arylesterase)          | 601250 | none found            |                           |
| PEPTIDE                 |        |                       |                           |
| METHIONINE              |        |                       |                           |
| SULFOXIDE               |        |                       |                           |
| REDUCTASE               |        |                       |                           |
| Peroxisome              | 170998 | NM_00503 <sub>6</sub> | none found                |
| proliferative activated |        |                       |                           |
| receptor, alpha/PPARA   |        |                       |                           |
| Peroxisome              | 600409 | NM_00623 <sub>8</sub> | none found                |
| proliferative activated |        |                       |                           |
| receptor, delta/PPARD   |        |                       |                           |
| Peroxisome              | 601487 | NM_00503 <sub>7</sub> | PRO115GLN                 |
| proliferative activated |        |                       |                           |
| receptor, gamma/PPARG   |        |                       |                           |
| Peroxisome              | 601487 | NM_00503 <sub>7</sub> | PRO12ALA                  |
| proliferative activated |        |                       |                           |
| receptor, gamma/PPARG   |        |                       |                           |
| Peroxisome              | 601487 | NM_00503 <sub>7</sub> | 1-BP DEL, 472A Frameshift |
| proliferative activated |        |                       |                           |
| receptor, gamma/PPARG   |        |                       |                           |
| Peroxisome              | 601487 | NM_00503 <sub>7</sub> | GLN286PRO                 |
| proliferative activated |        |                       |                           |
| receptor, gamma/PPARG   |        |                       |                           |
| Peroxisome              | 601487 | NM_00503 <sub>7</sub> | LYS319TER                 |
| proliferative activated |        |                       |                           |
| receptor, gamma/PPARG   |        |                       |                           |

|                                                                          |        |               |            |
|--------------------------------------------------------------------------|--------|---------------|------------|
| Peroxisome<br>proliferative activated<br>receptor,<br>gamma/PPARG        | 601487 | NM_00503<br>7 | ARG288HIS  |
| Phenol-preferring<br>sulfotransferase, family<br>1A, member<br>1/SULT1A1 | 171150 | NM_00105<br>5 | Arg213His  |
| Phenol-preferring<br>sulfotransferase, family<br>1A, member<br>2/SULT1A2 | 601292 | NM_00105<br>4 | none found |
| Phenol-preferring<br>sulfotransferase, family<br>1A, member<br>3/SULT1A3 | 600641 | L19956        | none found |
| phenylethanolamine N-<br>methyltransferase/PN<br>MT                      | 171190 | NM_00268<br>6 | BANI       |
| PHOSPHOADENOSI<br>NE-                                                    | 603262 |               | none found |
| PHOSPHOSULFATE<br>SYNTHETASE I                                           |        |               |            |
| Pyruvate<br>dehydrogenase<br>(lipoamide) beta                            | 179060 | M34479        | none found |
| RAR related orphan<br>receptor A/RORA                                    | 600825 | NM_00294<br>3 | none found |
| RAR related orphan<br>receptor C/RORC                                    | 602943 | NM_00506<br>0 | none found |
| reduced folate carrier                                                   | 600424 | U19720        | none found |

## RFC1

|                                                               |        |           |                                     |           |
|---------------------------------------------------------------|--------|-----------|-------------------------------------|-----------|
| renal microsomal dipeptidase/DPEP1 (b-lactam ring hydrolysis) | 179780 | NM_004413 | none found                          |           |
| renal transport of beta-amino acids/AABT                      | 109660 |           | none found                          |           |
| retinoic acid receptor alpha/RARA                             | 180240 | NM_000964 | 7-base deletion frameshift          |           |
| retinoic acid receptor alpha/RARA                             | 180240 | NM_000964 | codon 411 C to T                    |           |
| retinoic acid receptor alpha/RARA                             | 180240 | NM_000964 |                                     | Arg272Gln |
| retinoic acid receptor alpha/RARA                             | 180240 | NM_000964 |                                     | Met297Leu |
| retinoic acid receptor beta/RARB                              | 180220 | NM_000965 | none found                          |           |
| retinoic acid receptor gama/RARG                              | 180190 | M57707    | none found                          |           |
| retinoid X receptor alpha/RXRA                                | 180245 | NM_002957 | none found                          |           |
| retinoid X receptor beta/RXRB                                 | 180246 | X66424    | none found                          |           |
| retinoid X receptor gamma/RXRG                                | 180247 | U38480    | none found                          |           |
| serotonin transporter                                         | 182138 | X70697    | PstI promoter 44-bp ins/del         |           |
| serotonin transporter                                         | 182138 | X70697    | tandem repeat close to the promoter |           |
| serotonin transporter                                         | 182138 | X70697    | two polyadenylation sites           |           |

|                                                           |        |           |               |              |
|-----------------------------------------------------------|--------|-----------|---------------|--------------|
| serotonin transporter                                     | 182138 | X70697    | VNTR intron 2 | silent       |
| serotonin transporter                                     | 182138 | X70697    |               | polymorphism |
| Solute Carrier Family 1, Member 1; Slc1a1                 | 133550 | U08989    | none found    |              |
| Solute Carrier Family 1, Member 2; Slc1a2                 | 600300 | U03505    | none found    |              |
| Solute Carrier Family 1, Member 3; Slc1a3                 | 600111 | U03504    | none found    |              |
| Solute carrier family 1, member 4/SLC1A4 (glutamate)      | 600229 | NM_003038 | none found    |              |
| Solute carrier family 1, member 5/SLC1A5 (neutral AA)     | 109190 | AF105230  | none found    |              |
| Solute carrier family 1, member 6 (GABA/GLU)/SLC1A6       | 600637 | NM_005071 | none found    |              |
| Solute carrier family 10, member 1/SLC10A1 (taurocholate) | 182396 | NM_003049 | none found    |              |
| Solute carrier family 10, member 2/SLC10A2 (taurocholate) | 601295 | NM_000452 |               | LEU243PRO    |
| Solute carrier family 10, member 2/SLC10A2 (taurocholate) | 601295 | NM_000452 |               | THR262MET    |

|                                                                            |        |               |            |
|----------------------------------------------------------------------------|--------|---------------|------------|
| Solute carrier family<br>10, member<br>2/SLC10A2<br>(taurocholate)         | 601295 | NM_00045<br>2 | A171S      |
| Solute carrier family<br>12, member<br>2/SLC12A2<br>(dicarboxylic acids)   | 604148 | NM_00398<br>4 | none found |
| Solute carrier family<br>15, member<br>1/SLC15A1 (peptides)                | 600544 | U13173        | none found |
| Solute carrier family<br>15, member<br>2/SLC15A2 (peptides)                | 602339 | S78203        | none found |
| Solute carrier family<br>16, member<br>1/SLC16A1<br>(monocarboxylic acids) | 600682 | NM_00305<br>1 | none found |
| Solute carrier family<br>16, member<br>2/SLC16A2<br>(monocarboxylic acids) | 300095 | NM_00651<br>7 | none found |
| Solute carrier family<br>16, member<br>3/SLC16A3<br>(monocarboxylic acids) | 603877 | NM_00420<br>7 | none found |
| Solute carrier family<br>16, member<br>4/SLC16A4<br>(monocarboxylic acids) | 603878 | *****         | none found |
| Solute carrier family                                                      | 603879 | NM_00469      | none found |

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |        |           |            |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------|-----------|------------|
| 16, member<br>5/SLC16A5<br>(monocarboxylic acids)<br>Solute carrier family<br>16, member<br>6/SLC16A6<br>(monocarboxylic acids)<br>Solute carrier family<br>16, member<br>7/SLC16A7<br>(monocarboxylic acids)<br>Solute carrier family<br>21, member<br>2/SLC21A2<br>(prostaglandin)<br>Solute carrier family<br>21, member<br>3/SLC21A3 (organic<br>anion)<br>Solute carrier family<br>22, member 1-<br>like/SLC22A1 (organic<br>cation)<br>Solute carrier family<br>22, member 1-<br>like/SLC22A1 (organic<br>cation)<br>Solute carrier family<br>22, member<br>1/SLC22A2 (organic<br>cation) | 603880 | NM_004694 | none found |
| 5                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               | 603654 | AF049608  | none found |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 | 601460 | NM_005630 | none found |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 | 602883 | NM_005075 | none found |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 | 602631 | AF037064  | 111-BP INS |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 | 602631 | AF037064  | 688G-A     |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 | 602607 | NM_003058 | none found |

|                                                                      |        |               |                                                                           |           |
|----------------------------------------------------------------------|--------|---------------|---------------------------------------------------------------------------|-----------|
| Solute carrier family<br>22, member<br>2/SLC22A2 (organic<br>cation) | 602608 | NM_00305<br>8 |                                                                           |           |
| Solute carrier family<br>22, member<br>5/SLC22A5 (carnitine)         | 603377 |               | 113-BP DEL                                                                |           |
| Solute carrier family<br>22, member<br>5/SLC22A5 (carnitine)         | 603377 |               | 1-BP INS, 226C                                                            |           |
| Solute carrier family<br>22, member<br>5/SLC22A5 (carnitine)         | 603377 |               |                                                                           | TRP132TER |
| Solute carrier family<br>22, member<br>5/SLC22A5 (carnitine)         | 603377 |               | G-to-A transition in<br>the last nucleotide of<br>intron 8<br>1394-BP DEL |           |
| Solute carrier family<br>22, member<br>5/SLC22A5 (carnitine)         | 603377 |               | 19-BP INS                                                                 |           |
| Solute carrier family<br>22, member<br>5/SLC22A5 (carnitine)         | 603377 |               | 171-BP DEL                                                                |           |
| Solute carrier family<br>22, member<br>5/SLC22A5 (carnitine)         | 603377 |               |                                                                           | ARG282TER |
| Solute carrier family<br>22, member<br>5/SLC22A5 (carnitine)         | 603377 |               |                                                                           | TYR401TER |



|                                                                   |        |                 |            |
|-------------------------------------------------------------------|--------|-----------------|------------|
| Solute carrier family 22, member 5/SLC22A5 (carnitine)            | 603377 | 1-BP DEL, 1345G |            |
| Solute carrier family 22, member 5/SLC22A5 (carnitine)            | 603377 |                 | PRO478LEU  |
| Solute carrier family 22, member 5/SLC22A5 (carnitine)            | 603377 |                 | TYR211CYS  |
| Solute carrier family 22, member 5/SLC22A5 (carnitine)            | 603377 |                 | Arg169Gln  |
| Solute carrier family 25, member 1/SLC25A1 (tricarboxylic acids)  | 190315 | X96924          | none found |
| Solute carrier family 29 (nucleosides), member 1/SLC29A1/ENT1     | 602193 | NM_004955       | none found |
| Solute carrier family 29 (nucleosides), member 2/SLC29A2/ENT2     | 602110 | X86681          | none found |
| Solute carrier family 3 member 1/SLC3A1 (aa transporter)          | 104614 | *****           | none found |
| Solute carrier family 5 member 6/SLC5A6 (folate, biotin, lipoate) | 604024 | *****           | none found |
| Solute carrier family 6 (GABA), member 1/SLC6A1                   | 137165 | X54673          | none found |

|                                                              |        |               |                     |
|--------------------------------------------------------------|--------|---------------|---------------------|
| Solute carrier family 6<br>(betaine/GABA),<br>member 12      | 603080 | U27699        | none found          |
| Solute carrier family 6,<br>member                           | 163970 | NM_00104<br>3 | none found          |
| 5/SLC6A2/NAT1/NET<br>1 (glycine)                             |        |               |                     |
| Solute carrier family 6,<br>member 5/SLC6A5<br>(glycine)     | 604159 | NM_00421<br>1 | none found          |
| Solute carrier family 6,<br>member 6/SLC6A6<br>(taurine)     | 186854 | U16120        | Dinucleotide repeat |
| Solute carrier family 6,<br>Member 9; SLC6A9<br>(glycine)    | 601019 | S70612        | none found          |
| Solute carrier family 7,<br>member 1/SLC7A1<br>(cationic AA) | 104615 | *****         | TaqI                |
| Solute carrier family 7,<br>member 2/SLC7A2<br>(cationic AA) | 601872 | D29990        | none found          |
| Solute carrier family 7,<br>member 4/SLC7A4<br>(cationic AA) | 603752 | *****         | none found          |
| Solute carrier family 7,<br>member 5/SLC7A5<br>(neutral AA)  | 600182 | M80244        | none found          |
| Solute carrier family 7,<br>member 7/SLC7A7<br>(dibasic AA)  | 603593 | Y18474        | 1181, A-T, -2 A->T  |

|                                                             |        |        |                 |           |
|-------------------------------------------------------------|--------|--------|-----------------|-----------|
| Solute carrier family 7,<br>member 7/SLC7A7<br>(dibasic AA) | 603593 | Y18474 | 543-BP DEL      |           |
| Solute carrier family 7,<br>member 7/SLC7A7<br>(dibasic AA) | 603593 | Y18474 | 4-BP INS        |           |
| Solute carrier family 7,<br>member 9/SLC7A9<br>(neutral AA) | 604144 | *****  |                 | VAL170MET |
| Solute carrier family 7,<br>member 9/SLC7A9<br>(neutral AA) | 604144 | *****  |                 | GLY105ARG |
| Solute carrier family 7,<br>member 9/SLC7A9<br>(neutral AA) | 604144 | *****  |                 | ALA182THR |
| Solute carrier family 7,<br>member 9/SLC7A9<br>(neutral AA) | 604144 | *****  |                 | GLY195ARG |
| Solute carrier family 7,<br>member 9/SLC7A9<br>(neutral AA) | 604144 | *****  |                 | GLY259ARG |
| Solute carrier family 7,<br>member 9/SLC7A9<br>(neutral AA) | 604144 | *****  | 2-BP DEL, 596TG |           |
| Solute carrier family 7,<br>member 9/SLC7A9<br>(neutral AA) | 604144 | *****  | 1-BP INS, 520T  |           |
| sterol-O-acyl<br>transferase 1/SOAT1                        | 102642 | L21934 | none found      |           |
| sterol-O-acyl<br>transferase 2/SOAT2                        | 601311 | *****  | none found      |           |

|                                               |        |           |               |
|-----------------------------------------------|--------|-----------|---------------|
| Succinic semialdehyde dehydrogenase           | 271980 | L34820    | IVS9, G-T, +1 |
| Succinic semialdehyde dehydrogenase           | 271980 | L34820    | IVS5, G-A, +1 |
| SULFONYLUREA RECEPTOR 2                       | 601439 |           | none found    |
| Sulfotransferase, family 1C, member 3/SULT1C1 | 602385 | U66036    | none found    |
| Sulfotransferase, family 2B, member 1/SULT2B1 | 604125 | NM_004605 | none found    |
| Superoxide Dismutase 1/SOD1 (soluble)         | 147450 | NM_000454 | GLY37ARG      |
| Superoxide Dismutase 1/SOD1 (soluble)         | 147450 | NM_000454 | LEU38VAL      |
| Superoxide Dismutase 1/SOD1 (soluble)         | 147450 | NM_000454 | GLY41SER      |
| Superoxide Dismutase 1/SOD1 (soluble)         | 147450 | NM_000454 | GLY41ASP      |
| Superoxide Dismutase 1/SOD1 (soluble)         | 147450 | NM_000454 | HIS43ARG      |
| Superoxide Dismutase 1/SOD1 (soluble)         | 147450 | NM_000454 | GLY85ARG      |
| Superoxide Dismutase 1/SOD1 (soluble)         | 147450 | NM_000454 | GLY93CYS      |
| Superoxide Dismutase 1/SOD1 (soluble)         | 147450 | NM_000454 | GLY93ALA      |
| Superoxide Dismutase 1/SOD1 (soluble)         | 147450 | NM_000454 | GLU100GLY     |
| Superoxide Dismutase 1/SOD1 (soluble)         | 147450 | NM_000454 | LEU106VAL     |

|                      |        |          |                    |           |
|----------------------|--------|----------|--------------------|-----------|
| 1/SOD1 (soluble)     | 4      |          |                    | ILE113THR |
| Superoxide Dismutase | 147450 | NM_00045 |                    |           |
| 1/SOD1 (soluble)     | 4      |          |                    | ALA4VAL   |
| Superoxide Dismutase | 147450 | NM_00045 |                    |           |
| 1/SOD1 (soluble)     | 4      |          |                    | HIS46ARG  |
| Superoxide Dismutase | 147450 | NM_00045 |                    |           |
| 1/SOD1 (soluble)     | 4      |          |                    | ALA4THR   |
| Superoxide Dismutase | 147450 | NM_00045 |                    |           |
| 1/SOD1 (soluble)     | 4      |          |                    | ASP90ALA  |
| Superoxide Dismutase | 147450 | NM_00045 |                    |           |
| 1/SOD1 (soluble)     | 4      |          |                    | ILE104THE |
| Superoxide Dismutase | 147450 | NM_00045 |                    |           |
| 1/SOD1 (soluble)     | 4      |          |                    | LEU144SER |
| Superoxide Dismutase | 147450 | NM_00045 |                    |           |
| 1/SOD1 (soluble)     | 4      |          |                    | ALA145THR |
| Superoxide Dismutase | 147450 | NM_00045 |                    |           |
| 1/SOD1 (soluble)     | 4      |          |                    |           |
| Superoxide Dismutase | 147450 | NM_00045 | T-G, -10, 9-BP INS |           |
| 1/SOD1 (soluble)     | 4      |          |                    | CYS6PHE   |
| Superoxide Dismutase | 147450 | NM_00045 |                    |           |
| 1/SOD1 (soluble)     | 4      |          |                    | THR151ILE |
| Superoxide Dismutase | 147450 | NM_00045 |                    |           |
| 1/SOD1 (soluble)     | 4      |          |                    | GLU21LYS  |
| Superoxide Dismutase | 147450 | NM_00045 |                    |           |
| 1/SOD1 (soluble)     | 4      |          |                    | SER134ASN |
| Superoxide Dismutase | 147450 | NM_00045 |                    |           |
| 1/SOD1 (soluble)     | 4      |          |                    | LEU84VAL  |
| Superoxide Dismutase | 147450 | NM_00045 |                    |           |
| 1/SOD1 (soluble)     | 4      |          |                    | GLY16SER  |
| Superoxide Dismutase | 147450 | NM_00045 |                    |           |
| 1/SOD1 (soluble)     | 4      |          |                    |           |

|                                                                          |        |               |                 |
|--------------------------------------------------------------------------|--------|---------------|-----------------|
| Superoxide Dismutase<br>1/SOD1 (soluble)                                 | 147450 | NM_00045<br>4 | LEU126TER       |
| Superoxide Dismutase<br>1/SOD1 (soluble)                                 | 147450 | NM_00045<br>4 | VS4AS, A-G, -11 |
| Superoxide Dismutase<br>1/SOD1 (soluble)                                 | 147450 | NM_00045<br>4 | GLY72SER        |
| Superoxide Dismutase<br>1/SOD1 (soluble)                                 | 147450 | NM_00045<br>4 | Val7-->Glu      |
| Superoxide Dismutase<br>2/SOD2<br>(mitochondrial)                        | 147460 | X65965        | ALA16VAL        |
| Superoxide Dismutase<br>3/SOD3 (extracellular)                           | 185490 | NM_00310<br>2 | ARG213GLY       |
| Superoxide Dismutase<br>3/SOD3 (extracellular)                           | 185490 | NM_00310<br>2 | A24IG           |
| Superoxide Dismutase<br>3/SOD3 (extracellular)                           | 185490 | NM_00310<br>2 | C280T           |
| Thiopurine<br>methyltransferase (6-<br>mercaptopurine<br>detoxification) | 187680 | U12387        | ALA80PRO        |
| Thiopurine<br>methyltransferase (6-<br>mercaptopurine<br>detoxification) | 187680 | U12387        | ALA154THR       |
| Thiopurine<br>methyltransferase (6-<br>mercaptopurine<br>detoxification) | 187680 | U12387        | TYR240CYS       |
| Thiopurine<br>methyltransferase (6-<br>mercaptopurine<br>detoxification) | 187680 | U12387        | IVS9AS, G-A, -1 |

|                                                                          |        |        |               |
|--------------------------------------------------------------------------|--------|--------|---------------|
| mercaptapurine<br>detoxification)                                        | 187680 | U12387 | ALA154THR     |
| Thiopurine<br>methyltransferase (6-<br>mercaptapurine<br>detoxification) | 187680 | U12387 | TYR240CYS     |
| Thiopurine<br>methyltransferase (6-<br>mercaptapurine<br>detoxification) | 187680 | U12387 | ARG215HIS     |
| Thiopurine<br>methyltransferase (6-<br>mercaptapurine<br>detoxification) | 187680 | U12387 | G460 to A     |
| Thiopurine<br>methyltransferase (6-<br>mercaptapurine<br>detoxification) | 187680 | U12387 | A719 to G     |
| Thiopurine<br>methyltransferase (6-<br>mercaptapurine<br>detoxification) | 187680 | U12387 | VNTR promoter |
| Thiopurine<br>methyltransferase (6-<br>mercaptapurine<br>detoxification) | 187680 | U12387 | G644A         |
| Thiopurine<br>methyltransferase (6-<br>mercaptapurine<br>detoxification) | 187680 | U12387 | G238C         |

|                                                                                          |        |               |                              |              |
|------------------------------------------------------------------------------------------|--------|---------------|------------------------------|--------------|
| methytransferase (6-<br>mercaptopurine<br>detoxification)<br>Thiopurine                  | 187680 | U12387        | T681G                        |              |
| methytransferase (6-<br>mercaptopurine<br>detoxification)<br>Thiopurine                  | 187680 | U12387        | C-->T at nucleotide -<br>178 |              |
| methytransferase (6-<br>mercaptopurine<br>detoxification)<br>Thiopurine                  | 187680 | U12387        | T-->G681                     |              |
| methytransferase (6-<br>mercaptopurine<br>detoxification)<br>TRANSCRIPTION<br>FACTOR P65 | 164014 | L19067        |                              | 494, Glu-Asp |
| UDP<br>glycosyltransferase<br>1/UGT1                                                     | 191740 | NM_00107<br>2 | 13-BP DEL                    |              |
| UDP<br>glycosyltransferase<br>1/UGT1                                                     | 191740 | NM_00107<br>2 |                              | SER-PHE      |
| UDP<br>glycosyltransferase<br>1/UGT1                                                     | 191740 | NM_00107<br>2 |                              | GLN331TER    |
| UDP<br>glycosyltransferase<br>1/UGT1                                                     | 191740 | NM_00107<br>2 |                              | ARG341TER    |
| UDP<br>glycosyltransferase                                                               | 191740 | NM_00107<br>2 |                              | GLN331ARG    |



|                                      |        |               |                                |
|--------------------------------------|--------|---------------|--------------------------------|
| 1/UGT1                               | 191740 | NM_00107<br>2 | PHE170DEL                      |
| UDP<br>glycosyltransferase<br>1/UGT1 |        |               |                                |
| UDP<br>glycosyltransferase<br>1/UGT1 | 191740 | NM_00107<br>2 | SER376PHE                      |
| UDP<br>glycosyltransferase<br>1/UGT1 | 191740 | NM_00107<br>2 | GLY309GLU                      |
| UDP<br>glycosyltransferase<br>1/UGT1 | 191740 | NM_00107<br>2 | CYS-TER                        |
| UDP<br>glycosyltransferase<br>1/UGT1 | 191740 | NM_00107<br>2 | PRO229GLN                      |
| UDP<br>glycosyltransferase<br>1/UGT1 | 191740 | NM_00107<br>2 | 2-BP INS, TA,<br>TATAA ELEMENT |
| UDP<br>glycosyltransferase<br>1/UGT1 | 191740 | NM_00107<br>2 | 1-BP INS, 470T                 |
| UDP<br>glycosyltransferase<br>1/UGT1 | 191740 | NM_00107<br>2 | IVS1, G-C, +1                  |
| UDP<br>glycosyltransferase<br>1/UGT1 | 191740 | NM_00107<br>2 | 145C-T                         |
| UDP<br>glycosyltransferase<br>1/UGT1 | 191740 | NM_00107<br>2 | IVS3, A-G, -2                  |

|                                                               |        |               |            |           |
|---------------------------------------------------------------|--------|---------------|------------|-----------|
| UDP<br>glycosyltransferase<br>8/UGT8                          | 601291 | U30930        | none found |           |
| UDP<br>glycosyltransferase<br>family 2, member<br>B10/UGT2B10 | 600070 | NM_00107<br>5 | none found |           |
| UDP<br>glycosyltransferase<br>family 2, member<br>B15/UGT2B15 | 600069 | U06641        |            | asp85tyr  |
| UDP<br>glycosyltransferase<br>family 2, member<br>B17/UGT2B17 | 601903 | NM_00107<br>7 | none found |           |
| UDP<br>glycosyltransferase<br>family 2, member<br>B4/UGT2B4   | 600067 | NM_00107<br>3 |            | asp458glu |
| UDP<br>glycosyltransferase<br>family 2, member<br>B4/UGT2B4   | 600067 | NM_00107<br>3 |            | leu109phe |
| UDP<br>glycosyltransferase<br>family 2, member<br>B4/UGT2B4   | 600067 | NM_00107<br>3 |            | leu396phe |
| UDP<br>glycosyltransferase<br>family 2, member<br>B7/UGT2B7   | 600068 | NM_00107<br>4 | none found |           |

|                                          |        |           |            |
|------------------------------------------|--------|-----------|------------|
| UDP-glucuronosyltransferase <sup>e</sup> | 218800 | AJ005162  | none found |
| Vesicular acetylcholine transporter      | 600336 | NM_003055 | none found |
| Vesicular Amine Transporter 1; VAT1      | 193002 | *****     | none found |
| Vesicular Amine Transporter 2; VAT2      | 193001 | L09118    | TaqI XX    |

Table 21. Identified Variances in Genes or Related Pathways involved in Inflammation and Immune Disease

|                                                             |        |        |                        |
|-------------------------------------------------------------|--------|--------|------------------------|
| 3,5 cyclic nucleotide phosphodiesterase (HSPDE1A3A)         | 171890 | U40370 | none found             |
| activated leucocyte cell adhesion molecule/CD6 ligand/ALCAM | 601662 | L38608 | none found             |
| alpha-2-macroglobulin                                       | 103950 | M11313 | VAL1000ILE             |
| alpha-2-macroglobulin                                       | 103950 | M11313 | CYS972TYR              |
| alpha-2-macroglobulin                                       | 103950 | M11313 | deletion of the intron |
| alpha-2-macroglobulin                                       | 103950 | M11313 | ARG681HIS              |
| alpha-2-macroglobulin                                       | 103950 | M11313 | EX18DEL                |
| alpha-2-macroglobulin                                       | 103950 | M11313 | 5-BP DEL               |
| alpha-2-macroglobulin                                       | 103950 | M11313 | intronic               |

|                                          |        |        |                                           |            |
|------------------------------------------|--------|--------|-------------------------------------------|------------|
| alpha-2-macroglobulin                    | 103950 | M11313 | polymorphism<br>EcoRI                     | ILE333VAL  |
| antigen peptide transporter 1/MHC 1/TAP1 | 170260 | X57522 |                                           |            |
| antigen peptide transporter 1/MHC 1/TAP1 | 170260 | X57522 |                                           | ASP637GLY  |
| antigen peptide transporter 1/MHC 1/TAP1 | 170260 | X57522 |                                           | ARG659GLN  |
| antigen peptide transporter 1/MHC 1/TAP1 | 170260 | X57522 | 518 (GTC-->ATC)                           | Val-->Ile  |
| antigen peptide transporter 1/MHC 1/TAP1 | 170260 | X57522 | G-->T substitution in the promoter region |            |
| antigen peptide transporter 1/MHC 1/TAP1 | 170260 | X57522 | 10-bp insert in intron 9                  |            |
| antigen peptide transporter 1/MHC 1/TAP1 | 170260 | X57522 | G-->T 80bp 3' of termination codon        |            |
| antigen peptide transporter 2/MHC 2/TAP2 | 170261 | Z22935 |                                           | Ala665Thr  |
| antigen peptide transporter 2/MHC 2/TAP2 | 170261 | Z22935 |                                           | Gln687Stop |
| antigen peptide transporter 2/MHC 2/TAP2 | 170261 | Z22935 |                                           | ILE379VAL  |

SD-144141.1

|                      |        |        |                  |
|----------------------|--------|--------|------------------|
| 2/TAP2               | 147678 | X65019 | none found       |
| apoptosis-related    |        |        |                  |
| cystein protease     |        |        |                  |
| 1/interleukin 1-beta |        |        |                  |
| converting           |        |        |                  |
| enzyme/ICE/caspase   |        |        |                  |
| 1/CASP1              |        |        |                  |
| beta-1-adrenergic    | 109630 | J03019 | C1165G ARG389GLY |
| receptor; Adrb1      |        |        |                  |
| beta-1-adrenergic    | 109630 | J03019 | Bgl I.           |
| receptor; Adrb1      |        |        |                  |
| Beta-2-Adrenergic    | 109690 | M15169 | val 34 met       |
| Receptor; Adrb2      |        |        |                  |
| Beta-2-Adrenergic    | 109690 | M15169 | A-->G -1343      |
| Receptor; Adrb2      |        |        |                  |
| Beta-2-Adrenergic    | 109690 | M15169 | C-->G -468       |
| Receptor; Adrb2      |        |        |                  |
| Beta-2-Adrenergic    | 109690 | M15169 | G-->A -1023      |
| Receptor; Adrb2      |        |        |                  |
| Beta-2-Adrenergic    | 109690 | M15169 | G-->A -654       |
| Receptor; Adrb2      |        |        |                  |
| Beta-2-Adrenergic    | 109690 | M15169 | T-->A -1429      |
| Receptor; Adrb2      |        |        |                  |
| Beta-2-Adrenergic    | 109690 | M15169 | T-->C -367       |
| Receptor; Adrb2      |        |        |                  |
| Beta-2-Adrenergic    | 109690 | M15169 | Fnu4HI           |
| Receptor; Adrb2      |        |        |                  |
| Beta-2-Adrenergic    | 109690 | M15169 | T-->C -20        |
| Receptor; Adrb2      |        |        |                  |
| Beta-2-Adrenergic    | 109690 | M15169 | T-->C -47        |
| Receptor; Adrb2      |        |        |                  |

|                                                 |        |        |                      |
|-------------------------------------------------|--------|--------|----------------------|
| Beta-3-Adrenergic Receptor; Adrb3               | 109691 | X70811 | TRP64ARG             |
| Beta-3-Adrenergic Receptor; Adrb3               | 109691 | X70811 | intron 1 g1856t      |
| Beta-Adrenergic Receptor Kinase 2; Adrbk2       | 109636 | X69117 | none found           |
| bradykinin receptor B1/BDKRB1 G                 | 600337 | U12512 | 9-base pair deletion |
| protein-coupled bradykinin receptor B1/BDKRB1 G | 600337 | U12512 | A1098-->G            |
| protein-coupled bradykinin receptor B1/BDKRB1 G | 600337 | U12512 | C181-->T             |
| protein-coupled bradykinin receptor B1/BDKRB1 G | 600337 | U12512 | G-699-->C            |
| protein-coupled bradykinin receptor B2/BDKRB2 G | 113503 | X86164 | -845C/T              |
| protein-coupled bradykinin receptor B2/BDKRB2 G | 113503 | X86165 | -704C/T              |
| protein-coupled bradykinin receptor B2/BDKRB2 G | 113503 | X86166 | -649insG             |
| protein-coupled bradykinin receptor B2/BDKRB2 G | 113503 | X86167 | -640T/C              |

|                                                        |        |          |                                |           |
|--------------------------------------------------------|--------|----------|--------------------------------|-----------|
| bradykinin receptor<br>B2/BDKKRB2 G                    | 113503 | X86168   | -536C/T                        |           |
| protein-coupled<br>bradykinin receptor<br>B2/BDKKRB2 G | 113503 | X86169   | -412C/G                        |           |
| protein-coupled<br>bradykinin receptor<br>B2/BDKKRB2 G | 113503 | X86170   | -143C/T                        |           |
| protein-coupled<br>bradykinin receptor<br>B2/BDKKRB2 G | 113503 | X86171   | -78C/T                         |           |
| protein-coupled<br>bradykinin receptor<br>B2/BDKKRB2 G | 113503 | X86172   |                                | T21M      |
| protein-coupled<br>bradykinin receptor<br>B2/BDKKRB2 G | 113503 | X86173   | 9 bp de (-)21-29               |           |
| protein-coupled<br>bradykinin receptor<br>B2/BDKKRB2 G | 113503 | X86174   | C>T promoter 54                |           |
| protein-coupled<br>bradykinin receptor<br>B2/BDKKRB2 G | 113503 | X86175   | tandem repeat near<br>promoter |           |
| protein-coupled<br>bradykinin receptor<br>B2/BDKKRB2 G | 113503 | X86176   |                                | R14C      |
| protein-coupled<br>bradykinin receptor<br>B2/BDKKRB2 G | 113503 | X86177   | repeat 3'UTR                   |           |
| protein-coupled<br>Ca Channel alpha1a                  | 601011 | AF004884 |                                | ARG192GLN |

|                                                        |        |          |                                                                  |
|--------------------------------------------------------|--------|----------|------------------------------------------------------------------|
| (alt. splice) L-Type<br>Ca Channel alpha               | 601011 | AF004884 | THR666MET                                                        |
| (alt. splice) L-Type<br>Ca Channel alpha               | 601011 | AF004884 | VAL714ALA                                                        |
| (alt. splice) L-Type<br>Ca Channel alpha               | 601011 | AF004884 | ILE1811LEU                                                       |
| (alt. splice) L-Type<br>Ca Channel alpha               | 601011 | AF004884 | 1-BP DEL, 4073C frameshift                                       |
| (alt. splice) L-Type<br>Ca Channel alpha               | 601011 | AF004884 | G-to-A first<br>nucleotide of intron<br>24<br>(CAG) <sub>n</sub> |
| Ca Channel alpha<br>(alt. splice) L-Type               | 601011 | AF004884 | GLY293ARG                                                        |
| Ca Channel alpha<br>(alt. splice) L-Type               | 601011 | AF004884 | ASP715GLU                                                        |
| Ca Channel alpha<br>(alt. splice) L-Type               | 601011 | AF004884 | C4914T premature stop                                            |
| Ca Channel gamma L-Type                                | 114209 | L07738   | none found                                                       |
| Ca <sup>2+</sup> -dependent<br>phospholipase A2        | 601192 | U03090   | none found                                                       |
| CD3E antigen, epsilon<br>polypeptide (TiT3<br>complex) | 186830 | X03884   | T-to-C splice change                                             |
| CD3E antigen, epsilon<br>polypeptide (TiT3<br>complex) | 186830 | X03884   | TRP59TER                                                         |
| CD3E antigen, epsilon                                  | 186830 | X03884   | TaqI                                                             |



|                                                                     |        |          |            |
|---------------------------------------------------------------------|--------|----------|------------|
| polypeptide (TiT3 complex)                                          | 186740 | X04145   | MET1VAL    |
| CD3G antigen, gamma polypeptide (TiT3 complex)                      | 186740 | X04145   | 17-BP DEL  |
| CD3G antigen, gamma polypeptide (TiT3 complex)                      | 186740 | X04145   | Mspl       |
| Complement C1S component precursor (C1 esterase)                    | 120580 | J04080   | 4-BP DEL   |
| Cyclooxygenase 1 COX1                                               | 176805 | M59979   | none found |
| Cyclooxygenase 2 COX2                                               | 600262 | M90100   | none found |
| H.sapiens ACTH-R gene for adrenocorticotrophic hormone receptor     | None   | X65633   | none found |
| Histamine receptor H1                                               | 600167 | AF026261 | none found |
| Histamine receptor H2                                               | 142703 | M64799   | A649G      |
| Histamine receptor H3                                               | None   | U31332   | none found |
| Human DP prostanoid receptor (PTGDR) gene, 5 region and partial cds | 600022 | D38128   | none found |
| Human IP gene for prostacyclin receptor,                            |        |          |            |

|                                                                   |        |        |                            |
|-------------------------------------------------------------------|--------|--------|----------------------------|
| Human leukotriene-C4<br>synthase mRNA,<br>complete cds            | 246530 | U11552 | promoter<br>polymorphism   |
| Human mRNA for<br>prostacyclin synthase,<br>complete cds          | 601699 | D38145 | none found                 |
| Human prostaglandin<br>receptor ep1 subtype<br>mRNA, complete cds | 176802 | L22647 | none found                 |
| Intercellular adhesion<br>molecule 1                              | 147840 | M24283 | K/E 469                    |
| Intercellular adhesion<br>molecule 1                              | 147840 | M24283 | Dinucleotide repeat<br>3'  |
| Intercellular adhesion<br>molecule 2                              | 146630 | X15606 | none found                 |
| Intercellular adhesion<br>molecule 3                              | 146631 | X69819 | LYS29MET                   |
| interferon-gamma<br>receptor 2/IFNGR2                             | 147569 | U05875 | Gln64Arg                   |
| interferon-gamma<br>receptor 2/IFNGR2                             | 147569 |        | 2-BP DEL, AG,<br>NT278-279 |
| interferon-gamma<br>receptor 1/IFNGR1                             | 107470 | J03143 | 395C-A SER-TER             |
| interferon-gamma<br>receptor 1/IFNGR1                             | 107470 |        | 1-BP DEL frameshift        |
| interferon-gamma<br>receptor 1/IFNGR1                             | 107470 |        | ILE87THR                   |
| interferon-gamma<br>receptor 1/IFNGR1                             | 107470 |        | 4-BP INS, 107TTAC          |
| interferon-gamma                                                  | 107470 |        | G-A, +1                    |

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|                                                                   | Accession        | Gene             | Protein                 | Mutation  |
|-------------------------------------------------------------------|------------------|------------------|-------------------------|-----------|
| receptor 1/IFNGR1                                                 | 107470           | 4-BP DEL, NT818  | Val14Met                |           |
| interferon-gamma receptor 1/IFNGR1                                | 107470           |                  |                         |           |
| interferon-gamma receptor 1/IFNGR1                                | 107470           |                  | TaqI                    |           |
| interleukin 1 beta (IL1b)                                         | 147720           | K02770           | TaqI                    |           |
| interleukin 1 beta (IL1b)                                         | 147720           | K02770           | +5887 C --> T           |           |
| interleukin 1 beta (IL1b)                                         | 147720           | K02770           | exon 5 (position +3953) |           |
| interleukin 1 beta (IL1b)                                         | 147720           | K02770           | position -511           |           |
| Interleukin 1 receptor antagonist                                 | 147679           | X52015           | 86-bp tandem repeat     | Asp106Asn |
| Kallikrein Inhibitor Kallikrein KLK1                              | 147935<br>147910 | L19684<br>X13561 | none found<br>A1166-->C |           |
| Kallikrein KLK1                                                   | 147910           | X13561           | TaqI                    |           |
| Kallikrein KLK2                                                   | 147960           | S39329           | C to T at base 792      |           |
| L-Type Ca Channel alpha 2/delta                                   | 114204           | Z28613           | none found              |           |
| L-Type Ca Channel alpha d                                         | 114206           | Z26289           | none found              |           |
| L-type voltage dependent calcium channel alpha 1C subunit/CACNA1C | 114205           | M92269           | none found              |           |

|                                                                   |        |        |            |
|-------------------------------------------------------------------|--------|--------|------------|
| L-type voltage dependent calcium channel alpha 1S subunit/CACNA1S | 114208 | L33798 | ARG1086HIS |
| L-type voltage dependent calcium channel alpha 1S subunit/CACNA1S | 114208 | L33798 | ARG1239GLY |
| L-type voltage dependent calcium channel alpha 1S subunit/CACNA1S | 114208 | L33798 | ARG1239HIS |
| L-type voltage dependent calcium channel alpha 1S subunit/CACNA1S | 114208 | L33798 | ARG528HIS  |
| Leukocyte integrin alpha-4                                        | 192975 | L12002 | none found |
| Leukocyte integrin alpha-d                                        | 602453 | U40274 | none found |
| Leukocyte integrin alpha-l                                        | 153370 | Y00796 | none found |
| Leukocyte integrin alpha-m                                        | 120980 | J04145 | none found |
| Leukocyte integrin alpha-x                                        | 151510 | M81695 | none found |
| Leukocyte integrin beta-1                                         | 135630 | U28252 | none found |
| Leukocyte integrin beta-2                                         | 600065 | M15395 | ARG593CYS  |
| Leukocyte integrin                                                | 600065 | M15395 | LYS196THR  |

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|                              |        |        |                                 |
|------------------------------|--------|--------|---------------------------------|
| Leukocyte integrin<br>beta-2 | 600065 | M15395 | LEU149PRO                       |
| Leukocyte integrin<br>beta-2 | 600065 | M15395 | GLY169ARG                       |
| Leukocyte integrin<br>beta-2 | 600065 | M15395 | ATG-to-AAG initiation codon     |
| Leukocyte integrin<br>beta-2 | 600065 | M15395 | ARG586TRP                       |
| Leukocyte integrin<br>beta-2 | 600065 | M15395 | 12-bp insertion pro-ser-ser-gln |
| Leukocyte integrin<br>beta-2 | 600065 | M15395 | ASN351SER                       |
| Leukocyte integrin<br>beta-2 | 600065 | M15395 | PRO178LEU                       |
| Leukocyte integrin<br>beta-2 | 600065 | M15395 | ASP128ASN                       |
| Leukocyte integrin<br>beta-2 | 600065 | M15395 | G-A, splice/donor<br>site       |
| Leukocyte integrin<br>beta-2 | 600065 | M15395 | GLY284SER                       |
| Leukocyte integrin<br>beta-2 | 600065 | M15395 | SER138PRO                       |
| Leukocyte integrin<br>beta-2 | 600065 | M15395 | GLY273ARG                       |
| Leukocyte integrin<br>beta-2 | 600065 | M15395 | S138P                           |
| Leukocyte integrin<br>beta-2 | 173470 | M35999 | ARG214GLN                       |
| Leukocyte integrin<br>beta-3 | 173470 | M35999 | ASP119TYR                       |

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|                              |        |        |                 |
|------------------------------|--------|--------|-----------------|
| Leukocyte integrin<br>beta-3 | 173470 | M35999 | ARG214TRP       |
| Leukocyte integrin<br>beta-3 | 173470 | M35999 | SER752PRO       |
| Leukocyte integrin<br>beta-3 | 173470 | M35999 | ARG143GLN       |
| Leukocyte integrin<br>beta-3 | 173470 | M35999 | LEU33PRO        |
| Leukocyte integrin<br>beta-3 | 173470 | M35999 | PRO407ALA       |
| Leukocyte integrin<br>beta-3 | 173470 | M35999 | G-T, EXiDEL     |
| Leukocyte integrin<br>beta-3 | 173470 | M35999 | ARG489GLN       |
| Leukocyte integrin<br>beta-3 | 173470 | M35999 | CYS374TYR       |
| Leukocyte integrin<br>beta-3 | 173470 | M35999 | 11.2-KB DEL     |
| Leukocyte integrin<br>beta-3 | 173470 | M35999 | ARG724TER       |
| Leukocyte integrin<br>beta-3 | 173470 | M35999 | GLU616TER       |
| Leukocyte integrin<br>beta-4 | 147557 | X51841 | 1-BP INS, 3801T |
| Leukocyte integrin<br>beta-4 | 147557 | X51841 | 1-BP DEL, 1150G |
| Leukocyte integrin<br>beta-4 | 147557 | X51841 | LEU156PRO       |
| Leukocyte integrin<br>beta-4 | 147557 | X51841 | ARG554TER       |
| Leukocyte integrin<br>beta-4 | 147557 | X51841 | CYS61TYR        |

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|                                               |        |        |                    |
|-----------------------------------------------|--------|--------|--------------------|
| beta-4<br>Leukocyte integrin                  | 147557 | X51841 | CYS562ARG          |
| beta-4<br>Leukocyte integrin                  | 147557 | X51841 | IVS30DS, G-A, +1   |
| beta-4<br>Leukocyte integrin                  | 147557 | X51841 | TRP1478TER         |
| beta-4<br>Leukocyte integrin                  | 147557 | X51841 | CYS38ARG           |
| beta-4<br>Leukocyte integrin                  | 147557 | X51841 | 1-BP DEL, 4776G    |
| beta-4<br>Leukocyte integrin                  | 147557 | X51841 | 3434delT           |
| beta-4<br>Leukocyte integrin                  | 147557 | X51841 | 8-bp deletion      |
| beta-4<br>Leukocyte integrin                  | 147559 | M68892 | none found         |
| beta-7<br>Leukotriene A4<br>hydrolase         | 151570 | J03459 | none found         |
| Leukotriene C4<br>receptor                    |        |        | none found         |
| Leukotriene D4/E4<br>receptor                 |        |        | none found         |
| lipocortin 1/annexin 1                        | 151690 | X05908 | none found         |
| lipocortin 2/annexin 2                        | 151740 | D00017 | none found         |
| lipocortin 3/annexin 3                        | 106490 | M20560 | BglII              |
| lipocortin 3/annexin 3                        | 106490 | M20560 | SalI               |
| lipocortin 3/annexin 3                        | 106490 | M20560 | tandem repeat      |
| Lipoxygenases: 12-<br>lipoxygenase (platelet) | 152391 | M62982 | TAAA<br>none found |

|                                                             |        |        |            |
|-------------------------------------------------------------|--------|--------|------------|
| Lipoxygenases: 5-lipoxygenase (leukocytes)                  | 152390 | J03571 | none found |
| lymphotoxin beta receptor (TNFR superfamily, member 3/LTBR) | 600979 | L04270 | none found |
| N-acylamino acid aminohydrolase                             | 104620 | L07548 | none found |
| P2Y7                                                        | 601531 | D89078 | none found |
| purinoceptor/leukotriene B4 receptor/G protein-coupled      |        |        |            |
| Phospholipase A-2 (PLA-2) lung                              | 172410 | M21054 | none found |
| Phospholipase C beta-3                                      | 600230 | Z26649 | none found |
| Phospholipase C delta-1                                     | 602142 | U09117 | none found |
| Phospholipase C epsilon                                     | 600597 | D42108 | none found |
| Phospholipase C gamma-1                                     | 172420 | M34667 | none found |
| Phospholipase C gamma-2                                     | 600220 | M37238 | none found |
| Phospholipase C, beta 4                                     | 600810 | L41349 | none found |
| Platelet-activating factor receptor                         | 173393 | M76674 | none found |
| Prostaglandin 15-OH dehydrogenase (PGDH)                    | 601688 | J05594 | none found |

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|                                                                          |        |        |            |           |
|--------------------------------------------------------------------------|--------|--------|------------|-----------|
| Prostaglandin E<br>receptor 2 (subtype<br>EP2), 53kD                     | 601586 | L28175 | none found |           |
| Prostaglandin E<br>receptor 3 (subtype<br>EP3) {alternative<br>products} | 176806 | X83861 | none found |           |
| PROSTAGLANDIN<br>E2 RECEPTOR, EP2<br>SUBTYPE                             | 176804 | U19487 | none found |           |
| PROSTAGLANDIN F<br>RECEPTOR                                              | 600563 | L24470 | none found |           |
| PROSTAGLANDIN<br>F2 ALPHA<br>RECEPTOR                                    |        | U26664 | none found |           |
| prostaglandin<br>transporter hPGT                                        | 601460 | U70867 | none found |           |
| recombination<br>activating gene<br>1/RAG1                               | 179615 | M29474 |            | GLU722LYS |
| recombination<br>activating gene<br>1/RAG1                               | 179615 | M29474 |            | GLU774TER |
| recombination<br>activating gene<br>1/RAG1                               | 179615 | M29474 |            | TYR938TER |
| recombination<br>activating gene<br>1/RAG1                               | 179615 | M29474 |            | ALA156VAL |
| recombination<br>activating gene                                         | 179615 | M29474 |            | ARG56IHIS |

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|                                                      |        |        |                      |
|------------------------------------------------------|--------|--------|----------------------|
| 1/RAG1<br>recombination<br>activating gene<br>1/RAG1 | 179615 | M29474 | ARG396CYS            |
| recombination<br>activating gene<br>1/RAG1           | 179615 | M29474 | TYR912CYS            |
| recombination<br>activating gene<br>1/RAG1           | 179615 | M29474 | ARG396HIS            |
| recombination<br>activating gene<br>1/RAG1           | 179615 | M29474 | ASP429GLY            |
| recombination<br>activating gene<br>1/RAG1           | 179615 | M29474 | ARG561CYS            |
| recombination<br>activating gene<br>1/RAG1           | 179615 | M29474 | ARG737HIS            |
| recombination<br>activating gene<br>1/RAG1           | 179615 | M29474 | 13-BP DEL,<br>NT1723 |
| recombination<br>activating gene<br>1/RAG1           | 179615 | M29474 | 2-BP DEL, NT368      |
| recombination<br>activating gene<br>2/RAG2           | 179616 |        | CYS476TYR            |
| recombination<br>activating gene<br>2/RAG2           | 179616 |        | ARG220GLN            |

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|                                                                                                   |        |        |                            |           |  |
|---------------------------------------------------------------------------------------------------|--------|--------|----------------------------|-----------|--|
| recombination<br>activating gene<br>2/RAG2                                                        | 179616 |        |                            | CYS41TRP  |  |
| recombination<br>activating gene<br>2/RAG2                                                        | 179616 |        |                            | MET285ARG |  |
| regulator of G-protein<br>signalling 1/RGS1                                                       | 600323 | X73427 | none found                 |           |  |
| Retinoic acid receptor,<br>alpha/RARA                                                             | 180240 | X06538 | 7-base deletion frameshift |           |  |
| Retinoic acid receptor,<br>alpha/RARA                                                             | 180240 | X06538 |                            | Arg272Gln |  |
| Retinoic acid receptor,<br>alpha/RARA                                                             | 180240 | X06538 |                            | Met297Leu |  |
| Retinoic acid receptor,<br>alpha/RARA                                                             | 180240 | X06538 | codon 411 C to T           |           |  |
| Retinoic acid receptor,<br>beta/RARB                                                              | 180220 | X07282 | none found                 |           |  |
| Retinoic acid receptor,<br>gamma/RARG                                                             | 180190 | M24857 | none found                 |           |  |
| serotonin 5-HT<br>receptors 5-HT3, gated<br>ion channel                                           | 182139 | D49394 | none found                 |           |  |
| signaling lymphocytic<br>activation<br>molecule/SLAM                                              | 603492 | U33017 | none found                 |           |  |
| small inducible<br>cytokine subfamily A<br>(Cys-Cys), member<br>2/monocyte<br>chemotactic protein | 158105 | M28226 | -2518 (G or A)             |           |  |

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|                                                                                                                                        |        |        |                              |           |
|----------------------------------------------------------------------------------------------------------------------------------------|--------|--------|------------------------------|-----------|
| 1/MCP1/SCYA2<br>small inducible<br>cytokine subfamily A<br>(Cys-Cys), member<br>2/monocyte<br>chemotactic protein                      | 158105 | M28226 | -2076 (A or T)               |           |
| 1/MCP1/SCYA2<br>small inducible<br>cytokine subfamily A<br>(Cys-Cys), member<br>3/macrophage<br>inflammatory protein<br>1A/MIP1A/SCYA3 | 182283 | M25315 | none found                   |           |
| Solute carrier family 4,<br>anion exchanger,<br>member 1<br>(MEDIATES<br>EXCHANGE OF<br>INORGANIC<br>ANIONS ACROSS<br>THE MEMBRANE)    | 109270 | M27819 |                              | LYS56GLU  |
| Solute carrier family 4,<br>anion exchanger,<br>member 1<br>(MEDIATES<br>EXCHANGE OF<br>INORGANIC<br>ANIONS ACROSS<br>THE MEMBRANE)    | 109270 | M27819 | 24-BP DEL CODONS 400-<br>408 |           |
| Solute carrier family 4,<br>anion exchanger,                                                                                           | 109270 | M27819 |                              | PRO327ARG |

|                                                                                                                                     |        |        |           |
|-------------------------------------------------------------------------------------------------------------------------------------|--------|--------|-----------|
| member 1<br>(MEDIATES<br>EXCHANGE OF<br>INORGANIC<br>ANIONS ACROSS<br>THE MEMBRANE)<br>Solute carrier family 4,<br>anion exchanger, | 109270 | M27819 | GLU40LYS  |
| member 1<br>(MEDIATES<br>EXCHANGE OF<br>INORGANIC<br>ANIONS ACROSS<br>THE MEMBRANE)<br>Solute carrier family 4,<br>anion exchanger, | 109270 | M27819 | 10-BP DUP |
| member 1<br>(MEDIATES<br>EXCHANGE OF<br>INORGANIC<br>ANIONS ACROSS<br>THE MEMBRANE)<br>Solute carrier family 4,<br>anion exchanger, | 109270 | M27819 | GLU658LYS |
| member 1<br>(MEDIATES<br>EXCHANGE OF<br>INORGANIC<br>ANIONS ACROSS<br>THE MEMBRANE)<br>Solute carrier family 4,                     | 109270 | M27819 | GLY771ASP |

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|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------|--------|-----------|
| anion exchanger,<br>member 1<br>(MEDIATES<br>EXCHANGE OF<br>INORGANIC<br>ANIONS ACROSS<br>THE MEMBRANE)<br>Solute carrier family 4,<br>anion exchanger,<br>member 1<br>(MEDIATES<br>EXCHANGE OF<br>INORGANIC<br>ANIONS ACROSS<br>THE MEMBRANE)<br>Solute carrier family 4,<br>anion exchanger,<br>member 1<br>(MEDIATES<br>EXCHANGE OF<br>INORGANIC<br>ANIONS ACROSS<br>THE MEMBRANE)<br>Solute carrier family 4,<br>anion exchanger,<br>member 1<br>(MEDIATES<br>EXCHANGE OF<br>INORGANIC<br>ANIONS ACROSS<br>THE MEMBRANE) | 109270 | M27819 | GLN330TER |
| anion exchanger,<br>member 1<br>(MEDIATES<br>EXCHANGE OF<br>INORGANIC<br>ANIONS ACROSS<br>THE MEMBRANE)<br>Solute carrier family 4,<br>anion exchanger,<br>member 1<br>(MEDIATES<br>EXCHANGE OF<br>INORGANIC<br>ANIONS ACROSS<br>THE MEMBRANE)<br>Solute carrier family 4,<br>anion exchanger,<br>member 1<br>(MEDIATES<br>EXCHANGE OF<br>INORGANIC<br>ANIONS ACROSS<br>THE MEMBRANE)                                                                                                                                        | 109270 | M27819 | ARG150TER |
| anion exchanger,<br>member 1<br>(MEDIATES<br>EXCHANGE OF<br>INORGANIC<br>ANIONS ACROSS<br>THE MEMBRANE)<br>Solute carrier family 4,<br>anion exchanger,<br>member 1<br>(MEDIATES<br>EXCHANGE OF<br>INORGANIC<br>ANIONS ACROSS<br>THE MEMBRANE)                                                                                                                                                                                                                                                                               | 109270 | M27819 | 89G-A     |

|                                                                                                                                     |        |        |           |
|-------------------------------------------------------------------------------------------------------------------------------------|--------|--------|-----------|
| Solute carrier family 4,<br>anion exchanger,<br>member 1<br>(MEDIATES<br>EXCHANGE OF<br>INORGANIC<br>ANIONS ACROSS<br>THE MEMBRANE) | 109270 | M27819 | VAL557MET |
| Solute carrier family 4,<br>anion exchanger,<br>member 1<br>(MEDIATES<br>EXCHANGE OF<br>INORGANIC<br>ANIONS ACROSS<br>THE MEMBRANE) | 109270 | M27819 | ARG589HIS |
| Solute carrier family 4,<br>anion exchanger,<br>member 1<br>(MEDIATES<br>EXCHANGE OF<br>INORGANIC<br>ANIONS ACROSS<br>THE MEMBRANE) | 109270 | M27819 | ARG589CYS |
| Solute carrier family 4,<br>anion exchanger,<br>member 1<br>(MEDIATES<br>EXCHANGE OF<br>INORGANIC<br>ANIONS ACROSS<br>THE MEMBRANE) | 109270 | M27819 | SER613PHE |

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|                                                                                                                                                      |        |        |           |
|------------------------------------------------------------------------------------------------------------------------------------------------------|--------|--------|-----------|
| THE MEMBRANE)<br>Solute carrier family 4,<br>anion exchanger,<br>member 1<br>(MEDIATES<br>EXCHANGE OF<br>INORGANIC<br>ANIONS ACROSS<br>THE MEMBRANE) | 109270 | M27819 | ARG589SER |
| Solute carrier family 4,<br>anion exchanger,<br>member 1<br>(MEDIATES<br>EXCHANGE OF<br>INORGANIC<br>ANIONS ACROSS<br>THE MEMBRANE)                  | 109270 | M27819 | GLY701ASP |
| Solute carrier family 4,<br>anion exchanger,<br>member 1<br>(MEDIATES<br>EXCHANGE OF<br>INORGANIC<br>ANIONS ACROSS<br>THE MEMBRANE)                  | 109270 | M27819 | PRO854LEU |
| Solute carrier family 4,<br>anion exchanger,<br>member 1<br>(MEDIATES<br>EXCHANGE OF<br>INORGANIC<br>ANIONS ACROSS<br>THE MEMBRANE)                  | 109270 | M27819 | GLY130ARG |



| ANIONS ACROSS THE MEMBRANE)                                                                                    | 109270           | M27819           | THR837ALA               |
|----------------------------------------------------------------------------------------------------------------|------------------|------------------|-------------------------|
| Solute carrier family 4, anion exchanger, member 1 (MEDIATES EXCHANGE OF INORGANIC ANIONS ACROSS THE MEMBRANE) | 176947           | L05148           | GG-AG, -11              |
| T cell receptor-associated protein tyrosine kinase ZAP-70/ZAP70                                                | 176947           | L05148           | G-A, -9                 |
| T cell receptor-associated protein tyrosine kinase ZAP-70/ZAP70                                                | 176947           | L05148           | SER518ARG               |
| T cell receptor-associated protein tyrosine kinase ZAP-70/ZAP70                                                | 176947           | L05148           | 13-BP DEL frameshift    |
| Thromboxane A2 TP receptor, platelet and non-platelet                                                          | 188070           | U27325           | ARG60LEU                |
| Thromboxane synthase transforming growth                                                                       | 274180<br>190181 | M80646<br>L11695 | (CA)n intron 9<br>S387Y |

|                                                                                        |        |        |                                                             |  |
|----------------------------------------------------------------------------------------|--------|--------|-------------------------------------------------------------|--|
| factor, beta receptor I<br>(activin A receptor type<br>II-like kinase,<br>53kD)/TGFBRI | 190182 | M85079 | 2-BP INS frameshift                                         |  |
| transforming growth<br>factor, beta receptor II<br>(70-80kD)/TGFB2                     | 190182 | M85079 | THR315MET                                                   |  |
| transforming growth<br>factor, beta receptor II<br>(70-80kD)/TGFB2                     | 190182 | M85079 | GG to TT Stop codon                                         |  |
| transforming growth<br>factor, beta receptor II<br>(70-80kD)/TGFB2                     | 190182 | M85079 | a7g intron 2                                                |  |
| transforming growth<br>factor, beta receptor II<br>(70-80kD)/TGFB2                     | 190182 | M85079 | a-4t intron 3                                               |  |
| transforming growth<br>factor, beta receptor II<br>(70-80kD)/TGFB2                     | 190182 | M85079 | codon 128                                                   |  |
| transforming growth<br>factor, beta receptor II<br>(70-80kD)/TGFB2                     | 190182 | M85079 | ACA to GCA Thr to Ala                                       |  |
| transforming growth<br>factor, beta receptor II<br>(70-80kD)/TGFB2                     | 190182 | M85079 | base in the<br>polyadenine tract of<br>exon 3<br>none found |  |
| transforming growth<br>factor, beta receptor III<br>(betaglycan,                       | 600742 | L07594 |                                                             |  |

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|                                                  |        |        |                          |          |
|--------------------------------------------------|--------|--------|--------------------------|----------|
| 300kD)/TGFB $\beta$ 3                            |        |        |                          |          |
| tumor necrosis factor<br>alpha (TNFa)            | 191160 | X01394 | C-850T                   |          |
| tumor necrosis factor<br>alpha (TNFa)            | 191160 | X01394 | C-ins 5'UTR of exon<br>1 |          |
| tumor necrosis factor<br>alpha (TNFa)            | 191160 | X01394 | G -238 A                 |          |
| tumor necrosis factor<br>alpha (TNFa)            | 191160 | X01394 | G -376 A                 |          |
| tumor necrosis factor<br>alpha (TNFa)            | 191160 | X01394 | -1,031 T-->C             |          |
| tumor necrosis factor<br>alpha (TNFa)            | 191160 | X01394 | -863 C-->A               |          |
| tumor necrosis factor<br>alpha (TNFa)            | 191160 | X01394 | -308 G/A                 |          |
| tumor necrosis factor<br>alpha (TNFa)            | 191160 | X01394 |                          | ARG32TRP |
| tumor necrosis factor<br>alpha (TNFa)            | 191160 | X01394 |                          | LEU29SER |
| tumor necrosis factor<br>alpha (TNFa)            | 191160 | X01394 | G-376A                   |          |
| tumor necrosis factor<br>alpha (TNFa)            | 191160 | X01394 | NcoI                     |          |
| tumor necrosis factor<br>alpha (TNFa)            | 191160 | X01394 | C to T, -857T            |          |
| TUMOR NECROSIS<br>FACTOR RECEPTOR<br>1 PRECURSOR | 191190 | M58286 |                          | CYS33TYR |
| TUMOR NECROSIS<br>FACTOR RECEPTOR<br>1 PRECURSOR | 191190 | M58286 |                          | THR50MET |

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|                                                                           |        |        |            |
|---------------------------------------------------------------------------|--------|--------|------------|
| TUMOR NECROSIS<br>FACTOR RECEPTOR<br>1 PRECURSOR                          | 191190 | M58286 | CYS30ARG   |
| TUMOR NECROSIS<br>FACTOR RECEPTOR<br>1 PRECURSOR                          | 191190 | M58286 | CYS52PHE   |
| TUMOR NECROSIS<br>FACTOR RECEPTOR<br>1 PRECURSOR                          | 191190 | M58286 | CYS88ARG   |
| TUMOR NECROSIS<br>FACTOR RECEPTOR<br>1 PRECURSOR                          | 191190 | M58286 | CYS88TYR   |
| Tumor necrosis factor<br>receptor 2 (75kD)                                | 191191 | M32315 | M196R      |
| tumor necrosis factor<br>type 1 receptor<br>associated protein<br>(TRAP1) | None   | U12595 | none found |
| tumor necrosis factor<br>type 2 receptor<br>associated protein<br>(TRAP3) | 601895 | U12597 | none found |
| Vascular cell adhesion<br>molecule 1                                      | 192225 | M60335 | none found |
| vitamin D (1,25-<br>dihydroxyvitamin D3)<br>receptor/VDR                  | 601769 | J03258 | GLY30ASP   |
| vitamin D (1,25-<br>dihydroxyvitamin D3)<br>receptor/VDR                  | 601769 | J03258 | ARG-GLY    |
| vitamin D (1,25-<br>dihydroxyvitamin D3)<br>receptor/VDR                  | 601769 | J03258 | TYR292TER  |

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|                                                          |        |        |           |
|----------------------------------------------------------|--------|--------|-----------|
| dihydroxyvitamin D3)<br>receptor/VDR                     | 601769 | J03258 | ARG77GLN  |
| vitamin D (1,25-<br>dihydroxyvitamin D3)<br>receptor/VDR | 601769 | J03258 | ARG47GLN  |
| vitamin D (1,25-<br>dihydroxyvitamin D3)<br>receptor/VDR | 601769 | J03258 | GLN149TER |
| vitamin D (1,25-<br>dihydroxyvitamin D3)<br>receptor/VDR | 601769 | J03258 | ARG271LEU |
| vitamin D (1,25-<br>dihydroxyvitamin D3)<br>receptor/VDR | 601769 | J03258 | GLY46ASP  |
| vitamin D (1,25-<br>dihydroxyvitamin D3)<br>receptor/VDR | 601769 | J03258 | HIS305GLN |
| vitamin D (1,25-<br>dihydroxyvitamin D3)<br>receptor/VDR | 601769 | J03258 | ILE314SER |
| vitamin D (1,25-<br>dihydroxyvitamin D3)<br>receptor/VDR | 601769 | J03258 | ARG391CYS |
| vitamin D (1,25-<br>dihydroxyvitamin D3)<br>receptor/VDR | 601769 | J03258 | ARG30TER  |
| vitamin D (1,25-<br>dihydroxyvitamin D3)                 | 601769 | J03258 | BsmI      |

|                                                   |        |        |                             |
|---------------------------------------------------|--------|--------|-----------------------------|
| receptor/VDR                                      | 601769 | J03258 | ATG to ACG initiation codon |
| vitamin D (1,25-dihydroxyvitamin D3) receptor/VDR | 601769 | J03258 | Apa I                       |
| vitamin D (1,25-dihydroxyvitamin D3) receptor/VDR | 601769 | J03258 | Taq I                       |
| vitamin D (1,25-dihydroxyvitamin D3) receptor/VDR | 601769 | J03258 | codon 79 silent             |
| vitamin D (1,25-dihydroxyvitamin D3) receptor/VDR | 601769 | J03258 | base change in intron 3     |
| vitamin D (1,25-dihydroxyvitamin D3) receptor/VDR | 601769 | J03258 | EcoRV xx                    |

Table 22. Identified Variances in Genes or Related Pathways involved in Endocrine and Metabolic Disease

|                                           |        |        |            |
|-------------------------------------------|--------|--------|------------|
| 2,3-cyclic nucleotide 3-phosphodiesterase | M19650 | 123830 | none found |
| 3beta hydroxysteroid dehydrogenase        | M27137 | 109715 | none found |
| a-glucosidase                             | Y00839 | 232300 | EX18DEL    |

|                  |        |        |                   |            |
|------------------|--------|--------|-------------------|------------|
| a-glucosidase    | Y00839 | 232300 | 1-BP DEL          | frameshift |
| a-glucosidase    | Y00839 | 232300 | T-G, -13 intron 1 |            |
| a-glucosidase    | Y00839 | 232300 |                   | ARG725TRP  |
| a-glucosidase    | Y00839 | 232300 |                   | PRO545LEU  |
| a-glucosidase    | Y00839 | 232300 |                   | SER529VAL  |
| a-glucosidase    | Y00839 | 232300 |                   | GLY643ARG  |
| a-glucosidase    | Y00839 | 232300 |                   | GLU521LYS  |
| a-glucosidase    | Y00839 | 232300 |                   | GLU689LYS  |
| a-glucosidase    | Y00839 | 232300 |                   | ARG854TER  |
| a-glucosidase    | Y00839 | 232300 |                   | LEU299ARG  |
| a-glucosidase    | Y00839 | 232300 |                   | LYS903DEL  |
| a-glucosidase    | Y00839 | 232300 |                   | MET318THR  |
| a-glucosidase    | Y00839 | 232300 |                   | ASP91ASN   |
| a-glucosidase    | Y00839 | 232300 |                   | ASP645GLU  |
| a-glucosidase AB | D42041 | None   | none found        |            |
| ACAT1            | D90228 | 203750 | 1-BP INS, 1083A   |            |
| ACAT1            | D90228 | 203750 | 1163 + 2          |            |
| ACAT1            | D90228 | 203750 | 4-BP INS          |            |
| ACAT1            | D90228 | 203750 | 828 + 1           |            |
| ACAT1            | D90228 | 203750 | IVS10, A-C, -2    |            |
| ACAT1            | D90228 | 203750 | IVS10, G-C, -1    |            |
| ACAT1            | D90228 | 203750 | IVS8, G-T, +1     |            |
| ACAT1            | D90228 | 203750 |                   | ALA347THR  |
| ACAT1            | D90228 | 203750 |                   | GLY150ARG  |
| ACAT1            | D90228 | 203750 |                   | MET1LYS    |
| ACAT1            | D90228 | 203750 |                   | GLY379VAL  |
| ACAT1            | D90228 | 203750 |                   | GLN272TER  |
| ACAT1            | D90228 | 203750 |                   | GLU345DEL  |
| ACAT1            | D90228 | 203750 |                   | ASN93SER   |
| ACAT1            | D90228 | 203750 |                   | ILE312THR  |
| ACAT1            | D90228 | 203750 |                   | ALA333PRO  |

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|                                     |        |        |                             |                                                                           |
|-------------------------------------|--------|--------|-----------------------------|---------------------------------------------------------------------------|
| ACAT1                               | D90228 | 203750 | 1163 + 2<br>828 + 1<br>TaqI | N158D                                                                     |
| ACAT2                               | S70154 | 100678 |                             |                                                                           |
| ACAT2                               | S70154 | 100678 |                             |                                                                           |
| ACAT2                               | S70154 | 100678 |                             |                                                                           |
| ACAT2                               | S70154 | 100678 | 3804C-A                     | N158D<br>Q272X                                                            |
| ACAT2                               | S70154 | 100678 |                             |                                                                           |
| Adrenocorticotrophic hormone (ACTH) | M28636 | 176830 |                             |                                                                           |
| Adrenocorticotrophic hormone (ACTH) | M28636 | 176830 |                             |                                                                           |
| Adrenocorticotrophic hormone (ACTH) | M28636 | 176830 | 7133C DEL                   |                                                                           |
| aldose reductase                    | M34720 | 103880 |                             |                                                                           |
| Alpha Amylase 2A; pancreatic        | M28443 | 104650 |                             |                                                                           |
| androgen receptor                   | M20132 | 313700 |                             |                                                                           |
| androgen receptor                   | M20132 | 313700 | Hind III                    | silent<br>Gln>Ter<br>frameshift<br>frameshift<br><br>ala>thr<br>glu629arg |
| androgen receptor                   | M20132 | 313700 | (CAA)n                      |                                                                           |
| androgen receptor                   | M20132 | 313700 | (CAG)n                      |                                                                           |
| androgen receptor                   | M20132 | 313700 | (GGN)n                      |                                                                           |
| androgen receptor                   | M20132 | 313700 | 5-KB DEL, EX F, G           |                                                                           |
| androgen receptor                   | M20132 | 313700 | 5-KB DEL, EX E              |                                                                           |
| androgen receptor                   | M20132 | 313700 | C>T within exon B           |                                                                           |
| androgen receptor                   | M20132 | 313700 | CAG340TAG                   |                                                                           |
| androgen receptor                   | M20132 | 313700 | Del T at 3286               |                                                                           |
| androgen receptor                   | M20132 | 313700 | del1893                     |                                                                           |
| androgen receptor                   | M20132 | 313700 | G Codon 210 A               |                                                                           |
| androgen receptor                   | M20132 | 313700 | G Codon 211 A               |                                                                           |
| androgen receptor                   | M20132 | 313700 | G2314A                      |                                                                           |
| androgen receptor                   | M20132 | 313700 | G2677A                      |                                                                           |
| androgen receptor                   | M20132 | 313700 | HhaI                        |                                                                           |
| androgen receptor                   | M20132 | 313700 | HpaII                       |                                                                           |



|                   |        |        |                                                               |                |
|-------------------|--------|--------|---------------------------------------------------------------|----------------|
| androgen receptor | M20132 | 313700 | Insert of 69<br>nucleotides<br>MaeIII<br>PARTIAL DEL<br>Stu I | VAL730MET      |
| androgen receptor | M20132 | 313700 |                                                               | ALA721THR      |
| androgen receptor | M20132 | 313700 |                                                               | GLN902ARG      |
| androgen receptor | M20132 | 313700 |                                                               | HIS874TYR      |
| androgen receptor | M20132 | 313700 |                                                               | SER647ASN      |
| androgen receptor | M20132 | 313700 |                                                               | THR877SER      |
| androgen receptor | M20132 | 313700 |                                                               | ARG607GLN      |
| androgen receptor | M20132 | 313700 |                                                               | VAL865LEU      |
| androgen receptor | M20132 | 313700 |                                                               | VAL865MET      |
| androgen receptor | M20132 | 313700 |                                                               | LYS588TER      |
| androgen receptor | M20132 | 313700 |                                                               | CYS579PHE      |
| androgen receptor | M20132 | 313700 |                                                               | PHE582TYR      |
| androgen receptor | M20132 | 313700 |                                                               | pro892ser      |
| androgen receptor | M20132 | 313700 |                                                               | PRO546SER      |
| androgen receptor | M20132 | 313700 |                                                               | ILE869MET      |
| androgen receptor | M20132 | 313700 |                                                               | GLU2LYS        |
| androgen receptor | M20132 | 313700 |                                                               | ARG839CYS      |
| androgen receptor | M20132 | 313700 |                                                               | ARG839HIS      |
| androgen receptor | M20132 | 313700 |                                                               | GLN60TER       |
| androgen receptor | M20132 | 313700 |                                                               | TRP794TER      |
| androgen receptor | M20132 | 313700 |                                                               | LEU172TER      |
| androgen receptor | M20132 | 313700 |                                                               | LEU707ARG      |
| androgen receptor | M20132 | 313700 |                                                               | MET786VAL      |
| androgen receptor | M20132 | 313700 |                                                               | TYR761CYS      |
| androgen receptor | M20132 | 313700 |                                                               | ARG772CYS      |
| androgen receptor | M20132 | 313700 |                                                               | 598 or 599 ter |

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|                                            |          |        |                         |
|--------------------------------------------|----------|--------|-------------------------|
| androgen receptor                          | M20132   | 313700 | gly743val               |
| androgen receptor                          | M20132   | 313700 | Gln798Glu               |
| androgen receptor                          | M20132   | 313700 | arg726leu               |
| androgen receptor                          | M20132   | 313700 | LEU676PRO               |
| androgen receptor                          | M20132   | 313700 | ARG608LYS               |
| androgen receptor                          | M20132   | 313700 | val 581 phe             |
| androgen receptor                          | M20132   | 313700 | G214R                   |
| androgen receptor                          | M20132   | 313700 | THR877ALA               |
| androgen receptor                          | M20132   | 313700 | Arg615His               |
| androgen receptor                          | M20132   | 313700 | Arg752Gln               |
| androgen receptor                          | M20132   | 313700 | arg840his               |
| androgen receptor                          | M20132   | 313700 | ALA771THR               |
| androgen receptor                          | M20132   | 313700 | LYS882TER               |
| androgen receptor                          | M20132   | 313700 | ARG846HIS               |
| androgen receptor                          | M20132   | 313700 | ARG773HIS               |
| androgen receptor                          | M20132   | 313700 | TRP717TER               |
| androgen receptor                          | M20132   | 313700 | ARG773CYS               |
| androgen receptor                          | M20132   | 313700 | VAL866MET               |
| androgen receptor                          | M20132   | 313700 | ARG855HIS               |
| androgen receptor                          | M20132   | 313700 | MET780ILE               |
| Arginine Vasopressin<br>Receptor 1A/AVPR1A | AF030625 | 600821 | none found              |
| Arginine Vasopressin<br>Receptor 1B/AVPR1B | AF030512 | 600264 | none found              |
| Arginine vasopressin<br>receptor 2         | AF030626 | 304800 | 1-BP DEL                |
| Arginine vasopressin<br>receptor 2         | AF030626 | 304800 | 1-BP DEL, 102G          |
| Arginine vasopressin<br>receptor 2         | AF030626 | 304800 | 1-BP INS frameshift     |
| Arginine vasopressin                       | AF030626 | 304800 | 1-BP INS 804 frameshift |

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|                                 |          |        |                    |           |  |  |
|---------------------------------|----------|--------|--------------------|-----------|--|--|
| receptor 2                      |          |        |                    |           |  |  |
| Arginine vasopressin receptor 2 | AF030626 | 304800 | 15delC             |           |  |  |
| Arginine vasopressin receptor 2 | AF030626 | 304800 | 28-bp del          |           |  |  |
| Arginine vasopressin receptor 2 | AF030626 | 304800 | 786delG frameshift |           |  |  |
| Arginine vasopressin receptor 2 | AF030626 | 304800 | CpG dinucleotides  |           |  |  |
| Arginine vasopressin receptor 2 | AF030626 | 304800 |                    | TYR280CYS |  |  |
| Arginine vasopressin receptor 2 | AF030626 | 304800 |                    | P322H     |  |  |
| Arginine vasopressin receptor 2 | AF030626 | 304800 |                    | P322S     |  |  |
| Arginine vasopressin receptor 2 | AF030626 | 304800 |                    | ARG113TRP |  |  |
| Arginine vasopressin receptor 2 | AF030626 | 304800 |                    | TRP71TER  |  |  |
| Arginine vasopressin receptor 2 | AF030626 | 304800 |                    | ALA132ASP |  |  |
| Arginine vasopressin receptor 2 | AF030626 | 304800 |                    | ARG203CYS |  |  |
| Arginine vasopressin receptor 2 | AF030626 | 304800 |                    | GLY185CYS |  |  |
| Arginine vasopressin receptor 2 | AF030626 | 304800 |                    | TYR205CYS |  |  |
| Arginine vasopressin receptor 2 | AF030626 | 304800 |                    | ASP85ASN  |  |  |
| Arginine vasopressin receptor 2 | AF030626 | 304800 |                    | GLY201ASP |  |  |

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|                                                      |          |        |                 |
|------------------------------------------------------|----------|--------|-----------------|
| Arginine vasopressin receptor 2                      | AF030626 | 304800 | ARG337TER       |
| Arginine vasopressin receptor 2                      | AF030626 | 304800 | G107E           |
| Arginine vasopressin receptor 2                      | AF030626 | 304800 | L43P            |
| Arginine vasopressin receptor 2                      | AF030626 | 304800 | W193X           |
| Arginine vasopressin receptor 2                      | AF030626 | 304800 | ARG181CYS       |
| Arginine vasopressin receptor 2                      | AF030626 | 304800 | R137H           |
| ATP-sensitive inwardly rectifying K-channel          | U24660   | 600877 | none found      |
| Beta-3-Adrenergic Receptor; Adrb3                    | X70811   | 109691 | intron 1 g1856t |
| Beta-3-Adrenergic Receptor; Adrb3                    | X70811   | 109691 | TRP64ARG        |
| BONE MORPHOGENETIC PROTEIN RECEPTOR, TYPE IB; BMPR1B |          | 603248 | none found      |
| Calcitonin Receptor                                  | U26553   | 114131 | PRO463LEU       |
| Calcitonin Receptor                                  | U26553   | 114131 | pro447leu       |
| Calcitonin Related Peptide Receptor                  | U17473   | 114190 | none found      |
| Calcitonin Related Polypeptide Alpha                 | M26095   | 114130 | 1-BP INS, IVS4  |
| Calcium-activated                                    | U02632   | 600150 | none found      |

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|                                           |           |        |            |           |
|-------------------------------------------|-----------|--------|------------|-----------|
| potassium channel                         |           |        |            |           |
| calpain, large polypeptide L3/CAPN3       | NM_000070 | 114240 |            | ARG572GLN |
| calpain, large polypeptide L3/CAPN3       | NM_000070 | 114240 |            | ARG110TER |
| calpain, large polypeptide L3/CAPN3       | NM_000070 | 114240 |            | ARG769GLN |
| calpain, large polypeptide L3/CAPN3       | NM_000070 | 114240 |            | PRO319LEU |
| calpain, large polypeptide L3/CAPN3       | NM_000070 | 114240 |            | SER86PHE  |
|                                           |           |        | none found |           |
| Carnitine Acetyltransferase               | X78706    | 600184 |            |           |
| Carnitine Palmitoyltransferase I (muscle) | D87812    | 600528 |            | ASP454GLY |
| Carnitine Palmitoyltransferase II         | U09648    | 600650 | 413 delAG  |           |
| Carnitine Palmitoyltransferase II         | U09648    | 600650 |            | ARG631CYS |
| Carnitine Palmitoyltransferase II         | U09648    | 600650 |            | E174K     |
| Carnitine Palmitoyltransferase II         | U09648    | 600650 |            | F352C     |
| Carnitine Palmitoyltransferase II         | U09648    | 600650 |            | M647V     |

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|                                                                      |        |        |                           |
|----------------------------------------------------------------------|--------|--------|---------------------------|
| Carnitine                                                            | U09648 | 600650 | V368I                     |
| Palmitoyltransferase II                                              |        |        |                           |
| Carnitine                                                            | U09648 | 600650 | SER113LEU                 |
| Palmitoyltransferase II                                              |        |        |                           |
| Carnitine                                                            | U09648 | 600650 | R124Stop                  |
| Palmitoyltransferase II                                              |        |        |                           |
| Carnitine                                                            | U09648 | 600650 | ASP553ASN                 |
| Palmitoyltransferase II                                              |        |        |                           |
| Carnitine                                                            | U09648 | 600650 | PRO50HIS                  |
| Palmitoyltransferase II                                              |        |        |                           |
| Carnitine                                                            | U09648 | 600650 | GLU174LYS                 |
| Palmitoyltransferase II                                              |        |        |                           |
| Carnitine                                                            | U09648 | 600650 | PHE383TYR                 |
| Palmitoyltransferase II                                              |        |        |                           |
| Carnitine                                                            | U09648 | 600650 | F448L                     |
| Palmitoyltransferase II                                              |        |        |                           |
| Carnitine                                                            | U09648 | 600650 | G549D                     |
| Palmitoyltransferase II                                              |        |        |                           |
| Carnitine                                                            | U09648 | 600650 | ARG503CYS                 |
| Palmitoyltransferase II                                              |        |        |                           |
| Carnitine                                                            | U09648 | 600650 | TYR628SER                 |
| Palmitoyltransferase II                                              |        |        |                           |
| CCAA/T/ENHANCER-<br>BINDING PROTEIN,<br>GAMMA; CEBPG                 |        | 138972 | none found                |
| Cell surface receptor<br>for sulfonyleureas on<br>pancreatic b cells | L78207 | 600509 | EX35, G-A                 |
| Cell surface receptor<br>for sulfonyleureas on<br>pancreatic b cells | L78207 | 600509 | G-A, -9 EXON ALPHA<br>DEL |

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|                                                                      |        |        |                           |               |
|----------------------------------------------------------------------|--------|--------|---------------------------|---------------|
| Cell surface receptor<br>for sulfonyleureas on<br>pancreatic b cells | L78207 | 600509 | 3-BP DEL                  | PHE1388DEL    |
| Cell surface receptor<br>for sulfonyleureas on<br>pancreatic b cells | L78207 | 600509 | ACC-->ACT                 | Thr759Thr     |
| Cell surface receptor<br>for sulfonyleureas on<br>pancreatic b cells | L78207 | 600509 | BRANCH POINT,<br>A-G, -20 |               |
| Cell surface receptor<br>for sulfonyleureas on<br>pancreatic b cells | L78207 | 600509 | Exon 16 -3c-->t           |               |
| Cell surface receptor<br>for sulfonyleureas on<br>pancreatic b cells | L78207 | 600509 | G-A, -1                   | splice change |
| Cell surface receptor<br>for sulfonyleureas on<br>pancreatic b cells | L78207 | 600509 | G-A, -1 exon 5            |               |
| Cell surface receptor<br>for sulfonyleureas on<br>pancreatic b cells | L78207 | 600509 |                           | ARG1353PRO    |
| Cell surface receptor<br>for sulfonyleureas on<br>pancreatic b cells | L78207 | 600509 |                           | ARG1421CYS    |
| Cell surface receptor<br>for sulfonyleureas on<br>pancreatic b cells | L78207 | 600509 |                           | ARG1494TRP    |
| Cell surface receptor<br>for sulfonyleureas on<br>pancreatic b cells | L78207 | 600509 |                           | R275Q         |
| Cell surface receptor<br>for sulfonyleureas on<br>pancreatic b cells | L78207 | 600509 |                           | V560M         |

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|                                                                     |        |        |                     |
|---------------------------------------------------------------------|--------|--------|---------------------|
| for sulfonylureas on<br>pancreatic b cells                          | L78207 | 600509 | F591L               |
| Cell surface receptor<br>for sulfonylureas on<br>pancreatic b cells | L78207 | 600509 | G1382S              |
| Cell surface receptor<br>for sulfonylureas on<br>pancreatic b cells | L78207 | 600509 | H125Q               |
| Cell surface receptor<br>for sulfonylureas on<br>pancreatic b cells | L78207 | 600509 | N188S               |
| Cell surface receptor<br>for sulfonylureas on<br>pancreatic b cells | L78207 | 600509 | R1215Q              |
| Cell surface receptor<br>for sulfonylureas on<br>pancreatic b cells | L78207 | 600509 | R1394H              |
| Cell surface receptor<br>for sulfonylureas on<br>pancreatic b cells | L78207 | 600509 | T1139M              |
| Cell surface receptor<br>for sulfonylureas on<br>pancreatic b cells | L78207 | 600509 | S1370A              |
| Cell surface receptor<br>for sulfonylureas on<br>pancreatic b cells | L78207 | 600509 | GLY716VAL           |
| cytochrome P450<br>aromatase (CYP19)                                | X13589 | 107910 | (TTTA)n in intron 5 |



|                                                                                      |        |        |                                     |                                      |
|--------------------------------------------------------------------------------------|--------|--------|-------------------------------------|--------------------------------------|
| cytochrome P450<br>aromatase (CYP19)                                                 | X13589 | 107910 | 1-BP DEL, 408C                      | frameshift                           |
| cytochrome P450<br>aromatase (CYP19)                                                 | X13589 | 107910 | G-->A at Val80                      | silent                               |
| cytochrome P450<br>aromatase (CYP19)                                                 | X13589 | 107910 | G-1094 -A                           | ARG365GLN                            |
| cytochrome P450<br>aromatase (CYP19)                                                 | X13589 | 107910 | G-to-A                              | Val370-to-Met                        |
| cytochrome P450<br>aromatase (CYP19)                                                 | X13589 | 107910 | GT to AT exon and<br>intron 3       |                                      |
| cytochrome P450<br>aromatase (CYP19)                                                 | X13589 | 107910 | splice donor<br>(GT>GC) of intron 6 | 29 extra amino<br>acids<br>ARG435CYS |
| cytochrome P450<br>aromatase (CYP19)                                                 | X13589 | 107910 |                                     | CYS437TYR                            |
| cytochrome P450<br>aromatase (CYP19)                                                 | X13589 | 107910 |                                     | Arg264cys                            |
| cytochrome P450<br>aromatase (CYP19)                                                 | X13589 | 107910 |                                     | ARG375CYS                            |
| Cytochrome P450<br>reductase                                                         | S90469 | 124015 | none found                          |                                      |
| Cytochrome P450,<br>subfamily IIB<br>(phenobarbital-<br>inducible), polypeptide<br>6 | M29874 | None   | none found                          |                                      |
| Cytochrome P450,<br>subfamily XIA<br>(cholesterol side chain<br>cleavage)            | M14565 | 118485 | 5' UTR<br>pentanucleotide<br>repeat |                                      |

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|                                                                                     |        |        |                      |            |
|-------------------------------------------------------------------------------------|--------|--------|----------------------|------------|
| Cytochrome P450, subfamily XVII (steroid 17-alpha-hydroxylase), adrenal hyperplasia | M14564 | 202110 | 1-BP DEL             | frameshift |
| Cytochrome P450, subfamily XVII (steroid 17-alpha-hydroxylase), adrenal hyperplasia | M14564 | 202110 | 1-bp C del codon 131 |            |
| Cytochrome P450, subfamily XVII (steroid 17-alpha-hydroxylase), adrenal hyperplasia | M14564 | 202110 | 1-BP DEL             | frameshift |
| Cytochrome P450, subfamily XVII (steroid 17-alpha-hydroxylase), adrenal hyperplasia | M14564 | 202110 | 4-BP DUP, EX8        |            |
| Cytochrome P450, subfamily XVII (steroid 17-alpha-hydroxylase), adrenal hyperplasia | M14564 | 202110 | 469-BP INS           |            |
| Cytochrome P450, subfamily XVII (steroid 17-alpha-hydroxylase), adrenal hyperplasia | M14564 | 202110 | 518-BP DEL           |            |
| Cytochrome P450, subfamily XVII (steroid 17-alpha-hydroxylase), adrenal hyperplasia | M14564 | 202110 | 7-BP DUP, EX2        |            |

|                                                                                                  |        |        |                |           |
|--------------------------------------------------------------------------------------------------|--------|--------|----------------|-----------|
| subfamily XVII<br>(steroid 17-alpha-<br>hydroxylase), adrenal<br>hyperplasia                     | M14564 | 202110 | IVS2, G-T, +5  |           |
| Cytochrome P450,<br>subfamily XVII<br>(steroid 17-alpha-<br>hydroxylase), adrenal<br>hyperplasia | M14564 | 202110 | IVS7+5G to A   |           |
| Cytochrome P450,<br>subfamily XVII<br>(steroid 17-alpha-<br>hydroxylase), adrenal<br>hyperplasia | M14564 | 202110 | T-->C promoter |           |
| Cytochrome P450,<br>subfamily XVII<br>(steroid 17-alpha-<br>hydroxylase), adrenal<br>hyperplasia | M14564 | 202110 |                | ARG347HIS |
| Cytochrome P450,<br>subfamily XVII<br>(steroid 17-alpha-<br>hydroxylase), adrenal<br>hyperplasia | M14564 | 202110 |                | ARG358GLN |
| Cytochrome P450,<br>subfamily XVII<br>(steroid 17-alpha-<br>hydroxylase), adrenal<br>hyperplasia | M14564 | 202110 |                | TRP17TER  |

|                                                                                                                                               |        |        |              |
|-----------------------------------------------------------------------------------------------------------------------------------------------|--------|--------|--------------|
| (steroid 17-alpha-hydroxylase), adrenal hyperplasia<br>Cytochrome P450, subfamily XVII<br>(steroid 17-alpha-hydroxylase), adrenal hyperplasia | M14564 | 202110 | PHE417CYS    |
| Cytochrome P450, subfamily XVII<br>(steroid 17-alpha-hydroxylase), adrenal hyperplasia                                                        | M14564 | 202110 | PHE53/54 DEL |
| Cytochrome P450, subfamily XVII<br>(steroid 17-alpha-hydroxylase), adrenal hyperplasia                                                        | M14564 | 202110 | ARG239TER    |
| Cytochrome P450, subfamily XVII<br>(steroid 17-alpha-hydroxylase), adrenal hyperplasia                                                        | M14564 | 202110 | PRO342THR    |
| Cytochrome P450, subfamily XVII<br>(steroid 17-alpha-hydroxylase), adrenal hyperplasia                                                        | M14564 | 202110 | SER106PRO    |
| Cytochrome P450, subfamily XVII<br>(steroid 17-alpha-hydroxylase), adrenal hyperplasia                                                        | M14564 | 202110 | PHE53DEL     |

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|                                                                                                  |        |        |            |
|--------------------------------------------------------------------------------------------------|--------|--------|------------|
| hydroxylase), adrenal<br>hyperplasia                                                             | M14564 | 202110 | his373leu  |
| Cytochrome P450,<br>subfamily XVII<br>(steroid 17-alpha-<br>hydroxylase), adrenal<br>hyperplasia | M14564 | 202110 | Arg496Cys  |
| Cytochrome P450,<br>subfamily XVII<br>(steroid 17-alpha-<br>hydroxylase), adrenal<br>hyperplasia | M14564 | 202110 | Gln461Stop |
| Cytochrome P450,<br>subfamily XVII<br>(steroid 17-alpha-<br>hydroxylase), adrenal<br>hyperplasia | M14564 | 202110 | ARG96TRP   |
| Cytochrome P450,<br>subfamily XVII<br>(steroid 17-alpha-<br>hydroxylase), adrenal<br>hyperplasia | 603503 | 603503 | none found |
| DOLICHOL-<br>PHOSPHATE<br>MANNOSYLTRANSF<br>ERASE 1                                              | 603564 | 603564 | none found |
| DOLICHYL-<br>PHOSPHATE<br>MANNOSYLTRANSF<br>ERASE 2<br>REGULATORY                                |        |        |            |

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|                                            |           |        |                     |           |
|--------------------------------------------|-----------|--------|---------------------|-----------|
| SUBUNIT                                    |           |        |                     |           |
| Endothelin Receptor Type A                 | D90348    | 131243 | none found          |           |
| Endothelin Receptor Type B                 | L06623    | 131244 | 1-BP INS, 878T      |           |
| Endothelin Receptor Type B                 | L06623    | 131244 |                     | TRP275TER |
| Endothelin Receptor Type B                 | L06623    | 131244 |                     | ALA183GLY |
| Endothelin Receptor Type B                 | L06623    | 131244 |                     | TRP276CYS |
| Endothelin Receptor Type B                 | L06623    | 131244 |                     | SER305ASN |
| Endothelin Receptor Type B                 | L06623    | 131244 |                     | GLY57SER  |
| estrogen receptor 1 (ESR1)                 | X03635    | 133430 | RFLP (PssI enzyme)  |           |
| estrogen receptor 1 (ESR1)                 | X03635    | 133430 | RFLP (PvuII enzyme) |           |
| Estrogen-preferring sulfotransferase/STE   | NM_005420 | 600043 | none found          |           |
| FATTY ACID COENZYME A LIGASE, LONG-CHAIN 2 |           | 152426 | none found          |           |
| Folic Acid (Folate Receptor)               | M28099    | 136430 | none found          |           |
| follicle stimulating hormone-beta (FSH)    | M16646    | 136530 |                     | CYS51GLY  |
| follicle stimulating hormone-beta (FSH)    | M16646    | 136530 |                     | FS87TER   |

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|                                                |               |        |                                                           |                                           |
|------------------------------------------------|---------------|--------|-----------------------------------------------------------|-------------------------------------------|
| FSH receptor                                   | M65085        | 136435 | 566C-->T                                                  | ARG573CYS                                 |
| FSH receptor                                   | M65085        | 136435 | BsmI                                                      | ILE160THR                                 |
| FSH receptor                                   | M65085        | 136435 | HindIII                                                   | PHE591SER                                 |
| FSH receptor                                   | M65085        | 136435 | PstI                                                      | Thr307Ala                                 |
| FSH receptor                                   | M65085        | 136435 |                                                           | Asp567Gly                                 |
| FSH receptor                                   | M65085        | 136435 |                                                           | Ser680Asn                                 |
| FSH receptor                                   | M65085        | 136435 |                                                           | Asp334Gly                                 |
| FSH receptor                                   | M65085        | 136435 |                                                           | ALA189VAL                                 |
| G PROTEIN-<br>COUPLED<br>RECEPTOR 24;<br>GPR24 |               | 601751 | none found                                                |                                           |
| Glucagon                                       | J04040        | 138030 | Dinucleotide repeat                                       |                                           |
| glucagon<br>receptor/GCGR                      | NM_0001<br>60 | 138033 | Alu-repeat                                                |                                           |
| glucagon<br>receptor/GCGR                      | NM_0001<br>60 | 138033 |                                                           | GLY40SER                                  |
| glucagon-like peptide 1<br>receptor/GLP1R      | U01156        | 138032 | silent substitution in<br>exon 6                          |                                           |
| glucagon-like peptide 1<br>receptor/GLP1R      | U01156        | 138032 | simple tandem<br>repeat DNA<br>polymorphism<br>none found |                                           |
| glucagon-like peptide 2<br>receptor/GLP2R      | *****         | 603659 |                                                           |                                           |
| glucocorticoid receptor                        | M11050        | 138040 | 4-BP DEL                                                  | 2 bases of the<br>exon and the<br>first 2 |

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|                                                         |        |        |                                          |                                          |
|---------------------------------------------------------|--------|--------|------------------------------------------|------------------------------------------|
| glucocorticoid receptor                                 | M11050 | 138040 | A to G 3'-splice<br>junction of intron G | nucleotides of<br>intron 6<br>frameshift |
| glucocorticoid receptor                                 | M11050 | 138040 | Base-pair deletion in<br>exon 9          | 32 amino acid<br>deletion                |
| glucocorticoid receptor                                 | M11050 | 138040 | BcII                                     |                                          |
| glucocorticoid receptor                                 | M11050 | 138040 | T insertion 1188 and<br>1189             | frameshift                               |
| glucocorticoid receptor                                 | M11050 | 138040 | trinucleotide<br>insertion               | Arg453                                   |
| glucocorticoid receptor                                 | M11050 | 138040 | TthIII                                   |                                          |
| glucocorticoid receptor                                 | M11050 | 138040 |                                          | LEU753PHE                                |
| glucocorticoid receptor                                 | M11050 | 138040 |                                          | CYS736SER                                |
| glucocorticoid receptor                                 | M11050 | 138040 |                                          | CYS736THR                                |
| glucocorticoid receptor                                 | M11050 | 138040 |                                          | ILE747THR                                |
| glucocorticoid receptor                                 | M11050 | 138040 |                                          | ASP641VAL                                |
| glucocorticoid receptor                                 | M11050 | 138040 |                                          | L753F                                    |
| glucocorticoid receptor                                 | M11050 | 138040 |                                          | Q710X                                    |
| glucocorticoid receptor                                 | M11050 | 138040 |                                          | ASN363SER                                |
| glucocorticoid receptor                                 | U25029 | 138040 | none found                               |                                          |
| glucocorticoid receptor<br>alpha                        | X03348 | 138040 | none found                               |                                          |
| glucocorticoid receptor<br>beta                         |        |        | none found                               |                                          |
| GLUCOCORTICOID<br>RECEPTOR-<br>INTERACTING<br>PROTEIN 1 |        | 601993 | none found                               |                                          |
| glycogen synthase<br>[human, liver, mRNA,<br>2912 nt]   | S70004 | 138571 | IVS6, G-C, +1                            |                                          |



|                                                                                     |               |        |           |
|-------------------------------------------------------------------------------------|---------------|--------|-----------|
| glycogen synthase<br>[human, liver, mRNA,<br>2912 nt]                               | S70004        | 138571 | ALA339PRO |
| glycogen synthase<br>[human, liver, mRNA,<br>2912 nt]                               | S70004        | 138571 | ARG246TER |
| glycogen synthase<br>[human, liver, mRNA,<br>2912 nt]                               | S70004        | 138571 | ASN39SER  |
| glycogen synthase<br>[human, liver, mRNA,<br>2912 nt]                               | S70004        | 138571 | HIS446ASP |
| glycogen synthase<br>[human, liver, mRNA,<br>2912 nt]                               | S70004        | 138571 | MET491ARG |
| glycogen synthase<br>[human, liver, mRNA,<br>2912 nt]                               | S70004        | 138571 | SER483PRO |
| glycogen synthase<br>[human, liver, mRNA,<br>2912 nt]                               | S70004        | 138571 | PRO479GLN |
| gonadotropin releasing<br>hormone receptor/G<br>protein-<br>coupled/LHRHR/GNR<br>HR | NM_0004<br>06 | 138850 | ARG262GLN |
| gonadotropin releasing<br>hormone receptor/G<br>protein-<br>coupled/LHRHR/GNR<br>HR | NM_0004<br>06 | 138850 | GLN106ARG |

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|------------------------------------------------------------------------|-----------|--------|----------------------------|
| gonadotropin releasing hormone receptor/G protein-coupled/LHRHR/GNR HR | NM_000406 | 138850 | TYR284CYS                  |
| gonadotropin releasing hormone receptor/G protein-coupled/LHRHR/GNR HR | NM_000406 | 138850 | Mae III                    |
| Gonadotropin-releasing hormone (leutinizing-releasing hormone)         | M12578    | 152760 | none found                 |
| GROWTH FACTOR RECEPTOR-BOUND PROTEIN 2; GRB2                           |           | 108355 | none found                 |
| Growth hormone 1                                                       | V00519    | 139250 | G-T, +1 intron 4           |
| Growth hormone 1                                                       | V00519    | 139250 | 1-BP DEL, 371C             |
| Growth hormone 1                                                       | V00519    | 139250 | 18-BP DEL, +28-45 intron 3 |
| Growth hormone 1                                                       | V00519    | 139250 | FS132TER                   |
| Growth hormone 1                                                       | V00519    | 139250 | 2-BP DEL                   |
| Growth hormone 1                                                       | V00519    | 139250 | 6.7-KB DEL                 |
| Growth hormone 1                                                       | V00519    | 139250 | BglII                      |
| Growth hormone 1                                                       | V00519    | 139250 | G-A, +1 intron 3           |
| Growth hormone 1                                                       | V00519    | 139250 | G-A, +28                   |
| Growth hormone 1                                                       | V00519    | 139250 | G-C, +1 intron 3           |
| Growth hormone 1                                                       | V00519    | 139250 | G-C, +1 intron 4           |
| Growth hormone 1                                                       | V00519    | 139250 | HincII                     |
| Growth hormone 1                                                       | V00519    | 139250 | MspI                       |
| Growth hormone 1                                                       | V00519    | 139250 | T-C, +6 intron 3           |
| Growth hormone 1                                                       | V00519    | 139250 | ARG77CYS                   |

|                                                                   |        |        |                                    |
|-------------------------------------------------------------------|--------|--------|------------------------------------|
| Growth hormone 1                                                  | V00519 | 139250 | ASP112GLY                          |
| Growth hormone 1                                                  | V00519 | 139250 | TRP20TER                           |
| Growth hormone receptor                                           | X06562 | 600946 | none found                         |
| growth hormone releasing hormone receptor/G protein-coupled/GHRHR | U34195 | 139191 | IVS8DS, G-C, -1 alternative splice |
| growth hormone releasing hormone receptor/G protein-coupled/GHRHR | U34195 | 139191 | 1-BP DEL frameshift                |
| growth hormone releasing hormone receptor/G protein-coupled/GHRHR | U34195 | 139191 | 2-BP DEL frameshift                |
| growth hormone releasing hormone receptor/G protein-coupled/GHRHR | U34195 | 139191 | C to T codon 236. silent           |
| growth hormone releasing hormone receptor/G protein-coupled/GHRHR | U34195 | 139191 | EX4,6DEL                           |
| growth hormone releasing hormone receptor/G protein-coupled/GHRHR | U34195 | 139191 | GAA180GAG silent                   |
| growth hormone releasing hormone receptor/G protein-coupled/GHRHR | U34195 | 139191 | IVS4DS, G-A, +1 alternative splice |

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|----------------------------------------------------------------------------------------------|--------|--------|----------------------------|
| coupled/GHRHR<br>growth hormone<br>releasing hormone<br>receptor/G protein-<br>coupled/GHRHR | U34195 | 139191 | IVS6AS, G-T, -1            |
| growth hormone<br>releasing hormone<br>receptor/G protein-<br>coupled/GHRHR                  | U34195 | 139191 | IVS8AS, G-C, -1            |
| growth hormone<br>releasing hormone<br>receptor/G protein-<br>coupled/GHRHR                  | U34195 | 139191 | IVS9DS, G-A, +1 frameshift |
| growth hormone<br>releasing hormone<br>receptor/G protein-<br>coupled/GHRHR                  | U34195 | 139191 | ARG161CYS                  |
| growth hormone<br>releasing hormone<br>receptor/G protein-<br>coupled/GHRHR                  | U34195 | 139191 | GLU224ASP                  |
| growth hormone<br>releasing hormone<br>receptor/G protein-<br>coupled/GHRHR                  | U34195 | 139191 | GLU44LYS                   |
| growth hormone<br>releasing hormone<br>receptor/G protein-<br>coupled/GHRHR                  | U34195 | 139191 | PHE96SER                   |
| growth hormone<br>releasing hormone<br>receptor/G protein-<br>coupled/GHRHR                  | U34195 | 139191 | ASP152HIS                  |

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|                                                                   |        |        |           |
|-------------------------------------------------------------------|--------|--------|-----------|
| receptor/G protein-coupled/GHRHR growth hormone releasing hormone | U34195 | 139191 | GLN154PRO |
| receptor/G protein-coupled/GHRHR growth hormone releasing hormone | U34195 | 139191 | ILE153THR |
| receptor/G protein-coupled/GHRHR growth hormone releasing hormone | U34195 | 139191 | VAL155GLY |
| receptor/G protein-coupled/GHRHR growth hormone releasing hormone | U34195 | 139191 | VAL144ILE |
| receptor/G protein-coupled/GHRHR growth hormone releasing hormone | U34195 | 139191 | PRO131GLN |
| receptor/G protein-coupled/GHRHR growth hormone releasing hormone | U34195 | 139191 | GLU224TER |
| receptor/G protein-coupled/GHRHR growth hormone releasing hormone | U34195 | 139191 | P561T     |
| receptor/G protein-coupled/GHRHR growth hormone                   | U34195 | 139191 | ARG217TER |

|                                                                             |        |        |                 |
|-----------------------------------------------------------------------------|--------|--------|-----------------|
| releasing hormone<br>receptor/G protein-<br>coupled/GHRHR                   | U34195 | 139191 | ARG43TER        |
| growth hormone<br>releasing hormone<br>receptor/G protein-<br>coupled/GHRHR | U34195 | 139191 | CYS38TER        |
| growth hormone<br>releasing hormone<br>receptor/G protein-<br>coupled/GHRHR | L29177 |        | none found      |
| growth hormone-<br>releasing factor (GRF)                                   | X63282 | 601244 | none found      |
| Guanylate cyclase 1,<br>soluble, alpha 2                                    | X66534 | 139396 | none found      |
| Guanylate cyclase<br>soluble, alpha-3 chain                                 | X66533 | 139397 | none found      |
| Guanylate cyclase<br>soluble, beta-1 chain                                  | X65633 | 202200 | C818A           |
| H.sapiens ACTH-R<br>gene for<br>adrenocorticotrophic<br>hormone receptor    | X65633 | 202200 | Ser74Ile        |
| H.sapiens ACTH-R<br>gene for<br>adrenocorticotrophic<br>hormone receptor    | Z22535 | 601299 | none found      |
| H.sapiens ALK-3<br>mRNA                                                     | X64810 | 162150 | IVS5DS, A-C, +4 |
| H.sapiens encoding<br>PC1/PC3                                               |        |        |                 |

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|-----------------------------------------------------------------------------------------------|--------|--------|--------------------|
| H.sapiens encoding<br>PC1/PC3                                                                 | X64810 | 162150 | GLY483ARG          |
| H.sapiens HNF4<br>mRNA for hepatocyte<br>nuclear factor 4                                     | X76930 | 600281 | 1-BP DEL<br>PHE75T |
| H.sapiens HNF4<br>mRNA for hepatocyte<br>nuclear factor 4                                     | X76930 | 600281 | GLN268TER          |
| H.sapiens HNF4<br>mRNA for hepatocyte<br>nuclear factor 4                                     | X76930 | 600281 | ARG154TER          |
| H.sapiens HNF4<br>mRNA for hepatocyte<br>nuclear factor 4                                     | X76930 | 600281 | ARG127TRP          |
| H.sapiens HNF4<br>mRNA for hepatocyte<br>nuclear factor 4                                     | X76930 | 600281 | VAL393ILE          |
| H.sapiens HNF4<br>mRNA for hepatocyte<br>nuclear factor 4                                     | X76930 | 600281 | Val/Met255         |
| H.sapiens IL-1R2<br>mRNA for type II<br>interleukin-1 receptor,<br>(cell line CB23)           | X59770 | 147811 | none found         |
| H.sapiens mRNA for<br>beta subunit of<br>epithelial amiloride-<br>sensitive sodium<br>channel | X87159 | 600760 | 1-BP INS, 592C     |
| H.sapiens mRNA for<br>beta subunit of                                                         | X87159 | 600760 | 32-BP DEL          |

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|--|----------------------------------------------------------------------------------|--------|--------|---------------------|
|  | H.sapiens mRNA for epithelial amiloride-sensitive sodium channel                 | X87159 | 600760 | ARG564TER           |
|  | H.sapiens mRNA for beta subunit of epithelial amiloride-sensitive sodium channel | X87159 | 600760 | PRO616LEU           |
|  | H.sapiens mRNA for beta subunit of epithelial amiloride-sensitive sodium channel | X87159 | 600760 | GLY37SER            |
|  | H.sapiens mRNA for beta subunit of epithelial amiloride-sensitive sodium channel | X87159 | 600760 | TYR618HIS           |
|  | H.sapiens mRNA for beta subunit of epithelial amiloride-sensitive sodium channel | X87159 | 600760 | PRO615SER           |
|  | H.sapiens mRNA for carnitine carrier                                             | Y10319 | 212138 | I-BP INS frameshift |
|  | H.sapiens mRNA for                                                               | Y10319 | 212138 | 110-BP DEL          |



|                                                                                     |        |        |                                   |  |           |
|-------------------------------------------------------------------------------------|--------|--------|-----------------------------------|--|-----------|
| carnitine carrier                                                                   |        |        |                                   |  |           |
| H.sapiens mRNA for<br>carnitine carrier                                             | Y10319 | 212138 | 128-BP DEL                        |  |           |
| H.sapiens mRNA for<br>carnitine carrier                                             | Y10319 | 212138 |                                   |  | ARG166TER |
| H.sapiens mRNA for<br>carnitine carrier                                             | X82153 | 601105 |                                   |  | TER330TRP |
| H.sapiens mRNA for<br>cathepsin O                                                   | X82153 | 601105 |                                   |  | GLY146ARG |
| H.sapiens mRNA for<br>cathepsin O                                                   | X82153 | 601105 |                                   |  | ARG241TER |
| H.sapiens mRNA for<br>cathepsin O                                                   | X82153 | 601105 |                                   |  | ALA277VAL |
| H.sapiens mRNA for<br>cathepsin-O                                                   | X77383 | 600550 | none found                        |  |           |
| H.sapiens mRNA for<br>CCAAT/enhancer<br>binding protein alpha                       | Y11525 | 116897 | none found                        |  |           |
| H.sapiens mRNA for<br>cyclic nucleotide<br>phosphodiesterase                        | X95520 | 602047 | 1389 (A/G)                        |  |           |
| H.sapiens mRNA for<br>cyclic nucleotide<br>phosphodiesterase                        | X95520 | 602047 | dinucleotide repeat<br>introns 12 |  |           |
| H.sapiens mRNA for<br>cyclic nucleotide<br>phosphodiesterase                        | X95520 | 602047 | dinucleotide repeat<br>introns 5  |  |           |
| H.sapiens mRNA for<br>gamma subunit of<br>epithelial amiloride-<br>sensitive sodium | X87160 | 600761 | none found                        |  |           |

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|                                                                                           |        |        |  |                |
|-------------------------------------------------------------------------------------------|--------|--------|--|----------------|
| channel                                                                                   |        |        |  |                |
| H.sapiens mRNA for<br>GlcNac-1-P transferase                                              | Z82022 | 191350 |  | none found     |
| H.sapiens mRNA for<br>glucose-dependant<br>insulinotropic<br>polypeptide receptor<br>gene | X81832 | 147940 |  | 539G del       |
| H.sapiens mRNA for<br>glucose-dependant<br>insulinotropic<br>polypeptide receptor<br>gene | X81832 | 147940 |  | A-230C         |
| H.sapiens mRNA for<br>growth factor receptor<br>tyrosine kinase                           | X61656 | 191306 |  | none found     |
| H.sapiens mRNA for<br>microsomal<br>triglyceride transfer<br>protein                      | X75500 | 157147 |  | -164 T->C      |
| H.sapiens mRNA for<br>microsomal<br>triglyceride transfer<br>protein                      | X75500 | 157147 |  | -400 A-->T     |
| H.sapiens mRNA for<br>microsomal<br>triglyceride transfer<br>protein                      | X75500 | 157147 |  | -493T/G        |
| H.sapiens mRNA for<br>microsomal<br>triglyceride transfer                                 | X75500 | 157147 |  | 1-BP DEL, 215C |

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|---------------------------------------------------------------------------------|--------|--------|-----------------|-----------|
| protein<br>H.sapiens mRNA for<br>microsomal<br>triglyceride transfer<br>protein | X75500 | 157147 | IVS, G-A, +5    |           |
| H.sapiens mRNA for<br>microsomal<br>triglyceride transfer<br>protein            | X75500 | 157147 | IVS9AS, G-A, -1 |           |
| H.sapiens mRNA for<br>microsomal<br>triglyceride transfer<br>protein            | X75500 | 157147 |                 | ARG215TER |
| H.sapiens mRNA for<br>parathyroid hormone<br>receptor                           | X68596 | 168468 | 33-BP DEL       |           |
| H.sapiens mRNA for<br>parathyroid hormone<br>receptor                           | X68596 | 168468 |                 | HIS223ARG |
| H.sapiens mRNA for<br>parathyroid hormone<br>receptor                           | X68596 | 168468 |                 | THR410PRO |
| H.sapiens mRNA for<br>parathyroid hormone<br>receptor                           | X68596 | 168468 |                 | ARG383GLN |
| H.sapiens mRNA for<br>parathyroid hormone<br>receptor                           | X68596 | 168468 |                 | PRO132LEU |
| H.sapiens mRNA for<br>phosphoenolpyruvate<br>carboxykinase                      | X92720 | 261650 | none found      |           |

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|                                                               |        |        |                                 |           |
|---------------------------------------------------------------|--------|--------|---------------------------------|-----------|
| H.sapiens<br>oculorhombin<br>(aniridia) mRNA,<br>complete cds | M77844 | 106210 | IVS12DS, G-C, -1                |           |
| H.sapiens<br>oculorhombin<br>(aniridia) mRNA,<br>complete cds | M77844 | 106210 | 2-BP INS                        |           |
| H.sapiens<br>oculorhombin<br>(aniridia) mRNA,<br>complete cds | M77844 | 106210 | dinucleotide repeat<br>promoter |           |
| H.sapiens<br>oculorhombin<br>(aniridia) mRNA,<br>complete cds | M77844 | 106210 | EXON G DEL                      |           |
| H.sapiens<br>oculorhombin<br>(aniridia) mRNA,<br>complete cds | M77844 | 106210 | IVS10AS, A-T, -2                |           |
| H.sapiens<br>oculorhombin<br>(aniridia) mRNA,<br>complete cds | M77844 | 106210 | IVS11DS, A-G, -2                |           |
| H.sapiens<br>oculorhombin<br>(aniridia) mRNA,<br>complete cds | M77844 | 106210 |                                 | ARG103TER |
| H.sapiens<br>oculorhombin<br>(aniridia) mRNA,<br>complete cds | M77844 | 106210 |                                 | SER353TER |

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|-------------------------------------------------------------------------------|--------|--------|-----------|
| complete cds<br>H.sapiens<br>oculorhombin<br>(aniridia) mRNA,<br>complete cds | M77844 | 106210 | ARG26GLY  |
| H.sapiens<br>oculorhombin<br>(aniridia) mRNA,<br>complete cds                 | M77844 | 106210 | I29V      |
| H.sapiens<br>oculorhombin<br>(aniridia) mRNA,<br>complete cds                 | M77844 | 106210 | N17S      |
| H.sapiens<br>oculorhombin<br>(aniridia) mRNA,<br>complete cds                 | M77844 | 106210 | Q178H     |
| H.sapiens<br>oculorhombin<br>(aniridia) mRNA,<br>complete cds                 | M77844 | 106210 | R44Q      |
| H.sapiens<br>oculorhombin<br>(aniridia) mRNA,<br>complete cds                 | M77844 | 106210 | Q422R     |
| H.sapiens<br>oculorhombin<br>(aniridia) mRNA,<br>complete cds                 | M77844 | 106210 | ARG203TER |
| H.sapiens<br>oculorhombin<br>(aniridia) mRNA,<br>complete cds                 | M77844 | 106210 | ARG240TER |

|                                                                                                  |        |        |                       |
|--------------------------------------------------------------------------------------------------|--------|--------|-----------------------|
| (aniridia) mRNA,<br>complete cds<br>H.sapiens<br>oculorhombin                                    | M77844 | 106210 | GLY64VAL              |
| (aniridia) mRNA,<br>complete cds<br>H.sapiens<br>oculorhombin                                    | M77844 | 106210 | VAL126ASP             |
| (aniridia) mRNA,<br>complete cds<br>H.sapiens<br>oculorhombin                                    | M77844 | 106210 | GLN116TER             |
| (aniridia) mRNA,<br>complete cds<br>H.sapiens<br>oculorhombin                                    | M77844 | 106210 | I87R                  |
| (aniridia) mRNA,<br>complete cds<br>H.sapiens<br>oculorhombin                                    | M77844 | 106210 | ARG125CYS             |
| (aniridia) mRNA,<br>complete cds<br>H.sapiens<br>oculorhombin                                    | M77844 | 106210 | VAL54ASP              |
| H.sapiens PPP1R3<br>mRNA for protein<br>phosphatase 1,<br>glycogen-binding<br>regulatory subunit | X78578 | 600917 | 5-BP INS/DEL<br>3'UTR |

|                                                                                                                                                                                                                                          |               |        |                                         |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------|--------|-----------------------------------------|
| H.sapiens PPP1R3<br>mRNA for protein<br>phosphatase 1,<br>glycogen-binding<br>regulatory subunit<br>HEPATOCYTE<br>NUCLEAR FACTOR<br>3-BETA; HNF3B<br>HEPATOCYTE<br>NUCLEAR FACTOR<br>3-GAMMA; HNF3G<br>HEPATOCYTE<br>NUCLEAR FACTOR<br>6 | X78578        | 600917 | ASP905TYR                               |
|                                                                                                                                                                                                                                          |               | 600288 | none found                              |
|                                                                                                                                                                                                                                          |               | 602295 | none found                              |
|                                                                                                                                                                                                                                          |               | 604164 | none found                              |
| HMG CoA synthase<br>(HSH1) mitochondrial                                                                                                                                                                                                 | U12789        | 600234 | none found                              |
| HMG CoA synthase<br>soluble                                                                                                                                                                                                              | X66435        | 142940 | none found                              |
| HMGCoA<br>reductase/HMGCR                                                                                                                                                                                                                | NM_0008<br>59 | 142910 | HgiAI                                   |
| HMGCoA<br>reductase/HMGCR                                                                                                                                                                                                                | NM_0008<br>59 | 142910 | ScrFI polymorphism<br>in the 2nd intron |
| Homo sapiens (clone<br>lamda-hPEC-3)<br>phosphoenolpyruvate<br>carboxykinase (PCK1)<br>mRNA, complete cds                                                                                                                                | L05144        | 261680 | none found                              |
| Homo sapiens (clone<br>PEBP2aA1) core-<br>binding factor, runt<br>domain, alpha subunit                                                                                                                                                  | L40992        | 600211 | 16-BP INS                               |

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|                                                                                                             |          |        |            |           |
|-------------------------------------------------------------------------------------------------------------|----------|--------|------------|-----------|
| 1 (CBFA1) mRNA, 3' end of cds                                                                               | L40992   | 600211 | ALA REPEAT |           |
| Homo sapiens (clone PEBP2aA1) core-binding factor, runt domain, alpha subunit 1 (CBFA1) mRNA, 3' end of cds | L40992   | 600211 |            | MET175ARG |
| Homo sapiens (clone PEBP2aA1) core-binding factor, runt domain, alpha subunit 1 (CBFA1) mRNA, 3' end of cds | L40992   | 600211 |            | SER191ASN |
| Homo sapiens (clone PEBP2aA1) core-binding factor, runt domain, alpha subunit 1 (CBFA1) mRNA, 3' end of cds | L40992   | 600211 |            | TRP283TER |
| Homo sapiens acyl-CoA synthetase 4 (ACS4) mRNA, complete cds                                                | AF030555 | 300157 | none found |           |
| Homo sapiens low                                                                                            | M28219   | 143890 | ATn        |           |

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|-------------------------------------------------------------------------------------------------------------------------------|--------|--------|----------------|------------|
| density lipoprotein<br>receptor (FH 10 mutant<br>causing familial<br>hypercholesterolemia)<br>mRNA, 3 end                     | M28219 | 143890 | EX2-6DEL       |            |
| Homo sapiens low<br>density lipoprotein<br>receptor (FH 10 mutant<br>causing familial<br>hypercholesterolemia)<br>mRNA, 3 end | M28219 | 143890 | -19(CGG)n      |            |
| Homo sapiens low<br>density lipoprotein<br>receptor (FH 10 mutant<br>causing familial<br>hypercholesterolemia)<br>mRNA, 3 end | M28219 | 143890 | 1-BP DEL, 197G |            |
| Homo sapiens low<br>density lipoprotein<br>receptor (FH 10 mutant<br>causing familial<br>hypercholesterolemia)<br>mRNA, 3 end | M28219 | 143890 | 1061-8T-->C    |            |
| Homo sapiens low<br>density lipoprotein<br>receptor (FH 10 mutant<br>causing familial<br>hypercholesterolemia)<br>mRNA, 3 end | M28219 | 143890 | 1650delG       | frameshift |

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|-------------------------------------------------------------------------------------------------------------------------------|--------|--------|-----------------|
| receptor (FH 10 mutant<br>causing familial<br>hypercholesterolemia)<br>mRNA, 3 end                                            | M28219 | 143890 | 165delG         |
| Homo sapiens low<br>density lipoprotein<br>receptor (FH 10 mutant<br>causing familial<br>hypercholesterolemia)<br>mRNA, 3 end | M28219 | 143890 | 18-BP DUP       |
| Homo sapiens low<br>density lipoprotein<br>receptor (FH 10 mutant<br>causing familial<br>hypercholesterolemia)<br>mRNA, 3 end | M28219 | 143890 | 1846-1G-->A     |
| Homo sapiens low<br>density lipoprotein<br>receptor (FH 10 mutant<br>causing familial<br>hypercholesterolemia)<br>mRNA, 3 end | M28219 | 143890 | 2-BP DEL, 694AC |
| Homo sapiens low<br>density lipoprotein<br>receptor (FH 10 mutant<br>causing familial<br>hypercholesterolemia)<br>mRNA, 3 end | M28219 | 143890 | 2199delCA       |

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|-------------------------------------------------------------------------------------------------------------------------------|--------|--------|---------------|------------|
| causing familial<br>hypercholesterolemia)<br>mRNA, 3 end                                                                      | M28219 | 143890 | 2201delCA     |            |
| Homo sapiens low<br>density lipoprotein<br>receptor (FH 10 mutant<br>causing familial<br>hypercholesterolemia)<br>mRNA, 3 end | M28219 | 143890 | 313 + 1G-->A  |            |
| Homo sapiens low<br>density lipoprotein<br>receptor (FH 10 mutant<br>causing familial<br>hypercholesterolemia)<br>mRNA, 3 end | M28219 | 143890 | 335del10      | frameshift |
| Homo sapiens low<br>density lipoprotein<br>receptor (FH 10 mutant<br>causing familial<br>hypercholesterolemia)<br>mRNA, 3 end | M28219 | 143890 | 347delGCC     |            |
| Homo sapiens low<br>density lipoprotein<br>receptor (FH 10 mutant<br>causing familial<br>hypercholesterolemia)<br>mRNA, 3 end | M28219 | 143890 | 4-BP INS, EX8 | frameshift |

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|-------------------------------------------------------------------------------------------------------------------------------|--------|--------|-----------|------------|
| hypercholesterolemia)<br>mRNA, 3 end                                                                                          | M28219 | 143890 | 7-BP DEL  | frameshift |
| Homo sapiens low<br>density lipoprotein<br>receptor (FH 10 mutant<br>causing familial<br>hypercholesterolemia)<br>mRNA, 3 end | M28219 | 143890 | 785insG   |            |
| Homo sapiens low<br>density lipoprotein<br>receptor (FH 10 mutant<br>causing familial<br>hypercholesterolemia)<br>mRNA, 3 end | M28219 | 143890 | 9-BP DEL  |            |
| Homo sapiens low<br>density lipoprotein<br>receptor (FH 10 mutant<br>causing familial<br>hypercholesterolemia)<br>mRNA, 3 end | M28219 | 143890 | AGG450AGA | silent     |
| Homo sapiens low<br>density lipoprotein<br>receptor (FH 10 mutant<br>causing familial<br>hypercholesterolemia)<br>mRNA, 3 end | M28219 | 143890 | C766T     |            |

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|----------------------------------------------------------------------------------------------------------------------------------------------|--------|--------|------------|
| mRNA, 3 end<br>Homo sapiens low<br>density lipoprotein<br>receptor (FH 10 mutant<br>causing familial<br>hypercholesterolemia)<br>mRNA, 3 end | M28219 | 143890 | EX13-14DEL |
| Homo sapiens low<br>density lipoprotein<br>receptor (FH 10 mutant<br>causing familial<br>hypercholesterolemia)<br>mRNA, 3 end                | M28219 | 143890 | EX13-15DEL |
| Homo sapiens low<br>density lipoprotein<br>receptor (FH 10 mutant<br>causing familial<br>hypercholesterolemia)<br>mRNA, 3 end                | M28219 | 143890 | EX13-15DUP |
| Homo sapiens low<br>density lipoprotein<br>receptor (FH 10 mutant<br>causing familial<br>hypercholesterolemia)<br>mRNA, 3 end                | M28219 | 143890 | EX15DEL    |
| Homo sapiens low<br>density lipoprotein<br>receptor (FH 10 mutant<br>causing familial<br>hypercholesterolemia)<br>mRNA, 3 end                | M28219 | 143890 | EX16-17DEL |

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|----------------------------------------------------------------------------------------------------------------|--------|--------|------------|
| Homo sapiens low density lipoprotein receptor (FH 10 mutant causing familial hypercholesterolemia) mRNA, 3 end | M28219 | 143890 | EX16-18DEL |
| Homo sapiens low density lipoprotein receptor (FH 10 mutant causing familial hypercholesterolemia) mRNA, 3 end | M28219 | 143890 | EX16DEL    |
| Homo sapiens low density lipoprotein receptor (FH 10 mutant causing familial hypercholesterolemia) mRNA, 3 end | M28219 | 143890 | EX17-18DEL |
| Homo sapiens low density lipoprotein receptor (FH 10 mutant causing familial hypercholesterolemia) mRNA, 3 end | M28219 | 143890 | EX17DEL    |
| Homo sapiens low density lipoprotein receptor (FH 10 mutant causing familial hypercholesterolemia) mRNA, 3 end | M28219 | 143890 | EX2-12DEL  |
| Homo sapiens low density lipoprotein receptor (FH 10 mutant causing familial hypercholesterolemia) mRNA, 3 end | M28219 | 143890 | EX2-3DEL   |

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|-------------------------------------------------------------------------------------------------------------------------------|--------|--------|----------|
| density lipoprotein<br>receptor (FH 10 mutant<br>causing familial<br>hypercholesterolemia)<br>mRNA, 3 end                     | M28219 | 143890 | EX2-5DUP |
| Homo sapiens low<br>density lipoprotein<br>receptor (FH 10 mutant<br>causing familial<br>hypercholesterolemia)<br>mRNA, 3 end | M28219 | 143890 | EX2-8DUP |
| Homo sapiens low<br>density lipoprotein<br>receptor (FH 10 mutant<br>causing familial<br>hypercholesterolemia)<br>mRNA, 3 end | M28219 | 143890 | EX3-8DEL |
| Homo sapiens low<br>density lipoprotein<br>receptor (FH 10 mutant<br>causing familial<br>hypercholesterolemia)<br>mRNA, 3 end | M28219 | 143890 | EX4-6DEL |
| Homo sapiens low<br>density lipoprotein<br>receptor (FH 10 mutant<br>causing familial<br>hypercholesterolemia)<br>mRNA, 3 end | M28219 | 143890 | EX5DEL   |

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|-------------------------------------------------------------------------------------------------------------------------------|--------|--------|-----------|
| receptor (FH 10 mutant<br>causing familial<br>hypercholesterolemia)<br>mRNA, 3 end                                            | M28219 | 143890 | EX7-14DEL |
| Homo sapiens low<br>density lipoprotein<br>receptor (FH 10 mutant<br>causing familial<br>hypercholesterolemia)<br>mRNA, 3 end | M28219 | 143890 | EX7-8DEL  |
| Homo sapiens low<br>density lipoprotein<br>receptor (FH 10 mutant<br>causing familial<br>hypercholesterolemia)<br>mRNA, 3 end | M28219 | 143890 | EX7DEL    |
| Homo sapiens low<br>density lipoprotein<br>receptor (FH 10 mutant<br>causing familial<br>hypercholesterolemia)<br>mRNA, 3 end | M28219 | 143890 | EX9-10DEL |
| Homo sapiens low<br>density lipoprotein<br>receptor (FH 10 mutant<br>causing familial<br>hypercholesterolemia)<br>mRNA, 3 end | M28219 | 143890 | EX9DUP    |

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|-------------------------------------------------------------------------------------------------------------------------------|--------|--------|---------------|
| causing familial<br>hypercholesterolemia)<br>mRNA, 3 end                                                                      | M28219 | 143890 | HhaI intron 9 |
| Homo sapiens low<br>density lipoprotein<br>receptor (FH 10 mutant<br>causing familial<br>hypercholesterolemia)<br>mRNA, 3 end | M28219 | 143890 | HincII        |
| Homo sapiens low<br>density lipoprotein<br>receptor (FH 10 mutant<br>causing familial<br>hypercholesterolemia)<br>mRNA, 3 end | M28219 | 143890 | IVS3, G-A, +1 |
| Homo sapiens low<br>density lipoprotein<br>receptor (FH 10 mutant<br>causing familial<br>hypercholesterolemia)<br>mRNA, 3 end | M28219 | 143890 | IVS4, T-C, +2 |
| Homo sapiens low<br>density lipoprotein<br>receptor (FH 10 mutant<br>causing familial<br>hypercholesterolemia)<br>mRNA, 3 end | M28219 | 143890 | null allele   |

|                                                                                                                               |        |        |           |           |
|-------------------------------------------------------------------------------------------------------------------------------|--------|--------|-----------|-----------|
| hypercholesterolemia)<br>mRNA, 3 end                                                                                          | M28219 | 143890 | PvuII     |           |
| Homo sapiens low<br>density lipoprotein<br>receptor (FH 10 mutant<br>causing familial<br>hypercholesterolemia)<br>mRNA, 3 end | M28219 | 143890 | StuI      |           |
| Homo sapiens low<br>density lipoprotein<br>receptor (FH 10 mutant<br>causing familial<br>hypercholesterolemia)<br>mRNA, 3 end | M28219 | 143890 | T --> A28 |           |
| Homo sapiens low<br>density lipoprotein<br>receptor (FH 10 mutant<br>causing familial<br>hypercholesterolemia)<br>mRNA, 3 end | M28219 | 143890 |           | ALA410THR |
| Homo sapiens low<br>density lipoprotein<br>receptor (FH 10 mutant<br>causing familial<br>hypercholesterolemia)<br>mRNA, 3 end | M28219 | 143890 |           | VAL502MET |

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|----------------------------------------------------------------------------------------------------------------------------------------------|--------|--------|-----------|
| mRNA, 3 end<br>Homo sapiens low<br>density lipoprotein<br>receptor (FH 10 mutant<br>causing familial<br>hypercholesterolemia)<br>mRNA, 3 end | M28219 | 143890 | ASP283ASN |
| Homo sapiens low<br>density lipoprotein<br>receptor (FH 10 mutant<br>causing familial<br>hypercholesterolemia)<br>mRNA, 3 end                | M28219 | 143890 | GLY27DEL  |
| Homo sapiens low<br>density lipoprotein<br>receptor (FH 10 mutant<br>causing familial<br>hypercholesterolemia)<br>mRNA, 3 end                | M28219 | 143890 | GLU207LYS |
| Homo sapiens low<br>density lipoprotein<br>receptor (FH 10 mutant<br>causing familial<br>hypercholesterolemia)<br>mRNA, 3 end                | M28219 | 143890 | D154N     |
| Homo sapiens low<br>density lipoprotein<br>receptor (FH 10 mutant<br>causing familial<br>hypercholesterolemia)<br>mRNA, 3 end                | M28219 | 143890 | D206E     |

|                                                                                                                |        |        |           |
|----------------------------------------------------------------------------------------------------------------|--------|--------|-----------|
| Homo sapiens low density lipoprotein receptor (FH 10 mutant causing familial hypercholesterolemia) mRNA, 3 end | M28219 | 143890 | V408M     |
| Homo sapiens low density lipoprotein receptor (FH 10 mutant causing familial hypercholesterolemia) mRNA, 3 end | M28219 | 143890 | GLY197DEL |
| Homo sapiens low density lipoprotein receptor (FH 10 mutant causing familial hypercholesterolemia) mRNA, 3 end | M28219 | 143890 | C127W     |
| Homo sapiens low density lipoprotein receptor (FH 10 mutant causing familial hypercholesterolemia) mRNA, 3 end | M28219 | 143890 | C139G     |
| Homo sapiens low density lipoprotein receptor (FH 10 mutant causing familial hypercholesterolemia) mRNA, 3 end | M28219 | 143890 | E397X     |
| Homo sapiens low density lipoprotein receptor (FH 10 mutant causing familial hypercholesterolemia) mRNA, 3 end | M28219 | 143890 | GLN12TER  |

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|-------------------------------------------------------------------------------------------------------------------------------|--------|--------|-----------|
| density lipoprotein<br>receptor (FH 10 mutant<br>causing familial<br>hypercholesterolemia)<br>mRNA, 3 end                     | M28219 | 143890 | GLY525ASP |
| Homo sapiens low<br>density lipoprotein<br>receptor (FH 10 mutant<br>causing familial<br>hypercholesterolemia)<br>mRNA, 3 end | M28219 | 143890 | GLY528ASP |
| Homo sapiens low<br>density lipoprotein<br>receptor (FH 10 mutant<br>causing familial<br>hypercholesterolemia)<br>mRNA, 3 end | M28219 | 143890 | CYS163TYR |
| Homo sapiens low<br>density lipoprotein<br>receptor (FH 10 mutant<br>causing familial<br>hypercholesterolemia)<br>mRNA, 3 end | M28219 | 143890 | ASP206GLU |
| Homo sapiens low<br>density lipoprotein<br>receptor (FH 10 mutant<br>causing familial<br>hypercholesterolemia)<br>mRNA, 3 end | M28219 | 143890 | CYS646TYR |

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|-------------------------------------------------------------------------------------------------------------------------------|--------|--------|-----------|
| receptor (FH 10 mutant<br>causing familial<br>hypercholesterolemia)<br>mRNA, 3 end                                            | M28219 | 143890 | TRP66GLY  |
| Homo sapiens low<br>density lipoprotein<br>receptor (FH 10 mutant<br>causing familial<br>hypercholesterolemia)<br>mRNA, 3 end | M28219 | 143890 | SER156LEU |
| Homo sapiens low<br>density lipoprotein<br>receptor (FH 10 mutant<br>causing familial<br>hypercholesterolemia)<br>mRNA, 3 end | M28219 | 143890 | GLY544VAL |
| Homo sapiens low<br>density lipoprotein<br>receptor (FH 10 mutant<br>causing familial<br>hypercholesterolemia)<br>mRNA, 3 end | M28219 | 143890 | R329X     |
| Homo sapiens low<br>density lipoprotein<br>receptor (FH 10 mutant<br>causing familial<br>hypercholesterolemia)<br>mRNA, 3 end | M28219 | 143890 | ASN543HIS |

|                                                                                                                               |        |        |            |
|-------------------------------------------------------------------------------------------------------------------------------|--------|--------|------------|
| causing familial<br>hypercholesterolemia)<br>mRNA, 3 end                                                                      | M28219 | 143890 | ASPI54ASN  |
| Homo sapiens low<br>density lipoprotein<br>receptor (FH 10 mutant<br>causing familial<br>hypercholesterolemia)<br>mRNA, 3 end | M28219 | 143890 | N543H      |
| Homo sapiens low<br>density lipoprotein<br>receptor (FH 10 mutant<br>causing familial<br>hypercholesterolemia)<br>mRNA, 3 end | M28219 | 143890 | Glu119-Lys |
| Homo sapiens low<br>density lipoprotein<br>receptor (FH 10 mutant<br>causing familial<br>hypercholesterolemia)<br>mRNA, 3 end | M28219 | 143890 | C152R      |
| Homo sapiens low<br>density lipoprotein<br>receptor (FH 10 mutant<br>causing familial<br>hypercholesterolemia)<br>mRNA, 3 end | M28219 | 143890 | T705I      |

|                                                                                                                               |        |        |              |
|-------------------------------------------------------------------------------------------------------------------------------|--------|--------|--------------|
| hypercholesterolemia)<br>mRNA, 3 end                                                                                          | M28219 | 143890 | Cys297-->Phe |
| Homo sapiens low<br>density lipoprotein<br>receptor (FH 10 mutant<br>causing familial<br>hypercholesterolemia)<br>mRNA, 3 end |        |        |              |
| Homo sapiens low<br>density lipoprotein<br>receptor (FH 10 mutant<br>causing familial<br>hypercholesterolemia)<br>mRNA, 3 end | M28219 | 143890 | asp147his    |
| Homo sapiens low<br>density lipoprotein<br>receptor (FH 10 mutant<br>causing familial<br>hypercholesterolemia)<br>mRNA, 3 end |        |        |              |
| Homo sapiens low<br>density lipoprotein<br>receptor (FH 10 mutant<br>causing familial<br>hypercholesterolemia)<br>mRNA, 3 end | M28219 | 143890 | Trp469Stop   |
| Homo sapiens low<br>density lipoprotein<br>receptor (FH 10 mutant<br>causing familial<br>hypercholesterolemia)<br>mRNA, 3 end |        |        |              |
| Homo sapiens low<br>density lipoprotein<br>receptor (FH 10 mutant<br>causing familial<br>hypercholesterolemia)<br>mRNA, 3 end | M28219 | 143890 | ASP412HIS    |
| Homo sapiens low<br>density lipoprotein<br>receptor (FH 10 mutant<br>causing familial<br>hypercholesterolemia)<br>mRNA, 3 end |        |        |              |
| Homo sapiens low<br>density lipoprotein<br>receptor (FH 10 mutant<br>causing familial<br>hypercholesterolemia)<br>mRNA, 3 end | M28219 | 143890 | PRO664LEU    |



|                                                                                                                                              |        |        |              |
|----------------------------------------------------------------------------------------------------------------------------------------------|--------|--------|--------------|
| mRNA, 3 end<br>Homo sapiens low<br>density lipoprotein<br>receptor (FH 10 mutant<br>causing familial<br>hypercholesterolemia)<br>mRNA, 3 end | M28219 | 143890 | Ala370-->Thr |
| Homo sapiens low<br>density lipoprotein<br>receptor (FH 10 mutant<br>causing familial<br>hypercholesterolemia)<br>mRNA, 3 end                | M28219 | 143890 | C356-->Y     |
| Homo sapiens low<br>density lipoprotein<br>receptor (FH 10 mutant<br>causing familial<br>hypercholesterolemia)<br>mRNA, 3 end                | M28219 | 143890 | CYS240PHE    |
| Homo sapiens low<br>density lipoprotein<br>receptor (FH 10 mutant<br>causing familial<br>hypercholesterolemia)<br>mRNA, 3 end                | M28219 | 143890 | Asp200-->Gly |
| Homo sapiens low<br>density lipoprotein<br>receptor (FH 10 mutant<br>causing familial<br>hypercholesterolemia)<br>mRNA, 3 end                | M28219 | 143890 | C122X        |

|                                                                                                                |        |        |              |
|----------------------------------------------------------------------------------------------------------------|--------|--------|--------------|
| Homo sapiens low density lipoprotein receptor (FH 10 mutant causing familial hypercholesterolemia) mRNA, 3 end | M28219 | 143890 | Pro84-->Ser  |
| Homo sapiens low density lipoprotein receptor (FH 10 mutant causing familial hypercholesterolemia) mRNA, 3 end | M28219 | 143890 | pro664leu    |
| Homo sapiens low density lipoprotein receptor (FH 10 mutant causing familial hypercholesterolemia) mRNA, 3 end | M28219 | 143890 | Cys646-->Tyr |
| Homo sapiens low density lipoprotein receptor (FH 10 mutant causing familial hypercholesterolemia) mRNA, 3 end | M28219 | 143890 | Glu207-->Lys |
| Homo sapiens low density lipoprotein receptor (FH 10 mutant causing familial hypercholesterolemia) mRNA, 3 end | M28219 | 143890 | Trp66-->Gly  |
| Homo sapiens low density lipoprotein receptor (FH 10 mutant causing familial hypercholesterolemia) mRNA, 3 end | M28219 | 143890 | CYS660TER    |

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|-------------------------------------------------------------------------------------------------------------------------------|--------|--------|-----------|
| density lipoprotein<br>receptor (FH 10 mutant<br>causing familial<br>hypercholesterolemia)<br>mRNA, 3 end                     | M28219 | 143890 | TYR807CYS |
| Homo sapiens low<br>density lipoprotein<br>receptor (FH 10 mutant<br>causing familial<br>hypercholesterolemia)<br>mRNA, 3 end | M28219 | 143890 | TRP792TER |
| Homo sapiens low<br>density lipoprotein<br>receptor (FH 10 mutant<br>causing familial<br>hypercholesterolemia)<br>mRNA, 3 end | M28219 | 143890 | CYS210TER |
| Homo sapiens low<br>density lipoprotein<br>receptor (FH 10 mutant<br>causing familial<br>hypercholesterolemia)<br>mRNA, 3 end | M28219 | 143890 | GLY823ASP |
| Homo sapiens low<br>density lipoprotein<br>receptor (FH 10 mutant<br>causing familial<br>hypercholesterolemia)<br>mRNA, 3 end | M28219 | 143890 | LEU380HIS |

|                                                                                                                               |        |        |           |
|-------------------------------------------------------------------------------------------------------------------------------|--------|--------|-----------|
| receptor (FH 10 mutant<br>causing familial<br>hypercholesterolemia)<br>mRNA, 3 end                                            | M28219 | 143890 | TYR167TER |
| Homo sapiens low<br>density lipoprotein<br>receptor (FH 10 mutant<br>causing familial<br>hypercholesterolemia)<br>mRNA, 3 end | M28219 | 143890 | VAL408MET |
| Homo sapiens low<br>density lipoprotein<br>receptor (FH 10 mutant<br>causing familial<br>hypercholesterolemia)<br>mRNA, 3 end | M28219 | 143890 | C331C     |
| Homo sapiens low<br>density lipoprotein<br>receptor (FH 10 mutant<br>causing familial<br>hypercholesterolemia)<br>mRNA, 3 end | M28219 | 143890 | E119K     |
| Homo sapiens low<br>density lipoprotein<br>receptor (FH 10 mutant<br>causing familial<br>hypercholesterolemia)<br>mRNA, 3 end | M28219 | 143890 | N494 N    |

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|-------------------------------------------------------------------------------------------------------------------------------|--------|--------|-------|
| causing familial<br>hypercholesterolemia)<br>mRNA, 3 end                                                                      | M28219 | 143890 | T383P |
| Homo sapiens low<br>density lipoprotein<br>receptor (FH 10 mutant<br>causing familial<br>hypercholesterolemia)<br>mRNA, 3 end | M28219 | 143890 | T7051 |
| Homo sapiens low<br>density lipoprotein<br>receptor (FH 10 mutant<br>causing familial<br>hypercholesterolemia)<br>mRNA, 3 end | M28219 | 143890 | W23X  |
| Homo sapiens low<br>density lipoprotein<br>receptor (FH 10 mutant<br>causing familial<br>hypercholesterolemia)<br>mRNA, 3 end | M28219 | 143890 | W556S |
| Homo sapiens low<br>density lipoprotein<br>receptor (FH 10 mutant<br>causing familial<br>hypercholesterolemia)<br>mRNA, 3 end | M28219 | 143890 | W66G  |

|                                                                                  |          |        |                               |
|----------------------------------------------------------------------------------|----------|--------|-------------------------------|
| hypercholesterolemia)<br>mRNA, 3 end                                             | D89053   | 602371 | none found                    |
| Homo sapiens mRNA<br>for Acyl-CoA<br>synthetase 3, complete<br>cds               | AB006590 | 601663 | none found                    |
| Homo sapiens mRNA<br>for estrogen receptor<br>beta, complete cds                 | AB005293 | 170290 | none found                    |
| Homo sapiens mRNA<br>for perilipin, complete<br>cds                              | AJ006276 | 603652 | none found                    |
| Homo sapiens mRNA<br>for transient receptor<br>potential protein TRP6            | D88308   | 603247 | none found                    |
| Homo sapiens mRNA<br>for very-long-chain<br>acyl-CoA synthetase,<br>complete cds | AF066859 | 232600 | IVS14, G-A, +1, 67-<br>BP DEL |
| Homo sapiens muscle<br>glycogen<br>phosphorylase<br>(PYGM) mRNA,<br>complete cds | AF066859 | 232600 | ARG49TER                      |
| Homo sapiens muscle<br>glycogen<br>phosphorylase<br>(PYGM) mRNA,<br>complete cds | AF066859 | 232600 | GLY204SER                     |

|                                                                                  |          |        |           |
|----------------------------------------------------------------------------------|----------|--------|-----------|
| phosphorylase<br>(PYGM) mRNA,<br>complete cds<br>Homo sapiens muscle             | AF066859 | 232600 | LYS542THR |
| glycogen<br>phosphorylase<br>(PYGM) mRNA,<br>complete cds<br>Homo sapiens muscle | AF066859 | 232600 | METIGLY   |
| glycogen<br>phosphorylase<br>(PYGM) mRNA,<br>complete cds<br>Homo sapiens muscle | AF066859 | 232600 | GLU654LYS |
| glycogen<br>phosphorylase<br>(PYGM) mRNA,<br>complete cds<br>Homo sapiens muscle | AF066859 | 232600 | LEU396PRO |
| glycogen<br>phosphorylase<br>(PYGM) mRNA,<br>complete cds<br>Homo sapiens muscle | AF066859 | 232600 | GLY685ARG |
| glycogen<br>phosphorylase<br>(PYGM) mRNA,<br>complete cds<br>Homo sapiens muscle | AF066859 | 232600 | ARG575TER |

|                                                                                                                  |          |        |                  |
|------------------------------------------------------------------------------------------------------------------|----------|--------|------------------|
| (PYGM) mRNA,<br>complete cds<br>Homo sapiens muscle<br>glycogen<br>phosphorylase<br>(PYGM) mRNA,<br>complete cds | AF066859 | 232600 | GLN665GLU        |
| Homo sapiens muscle<br>glycogen<br>phosphorylase<br>(PYGM) mRNA,<br>complete cds                                 | AF066859 | 232600 | LYS753, DEL<br>A |
| Homo sapiens muscle<br>glycogen<br>phosphorylase<br>(PYGM) mRNA,<br>complete cds                                 | AF066859 | 232600 | METVAL           |
| Homo sapiens muscle<br>glycogen<br>phosphorylase<br>(PYGM) mRNA,<br>complete cds                                 | AF066859 | 232600 | GLU540TER        |
| Homo sapiens<br>somatostatin receptor<br>(SSTR4) gene,<br>complete cds                                           | L07833   | 182454 | none found       |
| Homo sapiens sorbitol<br>dehydrogenase gene,<br>complete cds                                                     | U07361   | 182500 | none found       |
| HOMOLOG OF<br>SONIC HEDGEHOG                                                                                     |          | 600725 | GLY31ARG         |

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|                                                                    |               |                    |
|--------------------------------------------------------------------|---------------|--------------------|
| HOMOLOG OF<br>SONIC HEDGEHOG                                       | 600725        | GLN100TER          |
| HOMOLOG OF<br>SONIC HEDGEHOG                                       | 600725        | LYS105TER          |
| HOMOLOG OF<br>SONIC HEDGEHOG                                       | 600725        | TRP117GLY          |
| HOMOLOG OF<br>SONIC HEDGEHOG                                       | 600725        | TRP117ARG          |
| Human (HepG2)<br>glucose transporter<br>gene mRNA, complete<br>cds | K03195 138140 | GCT15GCC<br>silent |
| Human (HepG2)<br>glucose transporter<br>gene mRNA, complete<br>cds | K03195 138140 | XbaI               |
| Human (HepG2)<br>glucose transporter<br>gene mRNA, complete<br>cds | K03195 138140 | DEL                |
| Human (HepG2)<br>glucose transporter<br>gene mRNA, complete<br>cds | K03195 138140 | LYS456TER          |
| Human (HepG2)<br>glucose transporter<br>gene mRNA, complete<br>cds | K03195 138140 | TYR449TER          |
| Human activin<br>receptor-like kinase<br>(ALK-5) mRNA,             | L11695 190181 | S387Y              |

|                                                          |        |        |         |           |
|----------------------------------------------------------|--------|--------|---------|-----------|
| complete cds                                             |        |        |         |           |
| Human bek mRNA for fibroblast growth factor receptor-BEK | X52832 | 176943 | ALU INS |           |
| Human bek mRNA for fibroblast growth factor receptor-BEK | X52832 | 176943 |         | CYS342TYR |
| Human bek mRNA for fibroblast growth factor receptor-BEK | X52832 | 176943 |         | CYS342ARG |
| Human bek mRNA for fibroblast growth factor receptor-BEK | X52832 | 176943 |         | CYS342SER |
| Human bek mRNA for fibroblast growth factor receptor-BEK | X52832 | 176943 |         | TYR340HIS |
| Human bek mRNA for fibroblast growth factor receptor-BEK | X52832 | 176943 |         | SER354CYS |
| Human bek mRNA for fibroblast growth factor receptor-BEK | X52832 | 176943 |         | ALA344ALA |
| Human bek mRNA for fibroblast growth factor receptor-BEK | X52832 | 176943 |         | ALA344GLY |
| Human bek mRNA for fibroblast growth factor receptor-BEK | X52832 | 176943 |         | TYR328CYS |
| Human bek mRNA for fibroblast growth factor receptor-BEK | X52832 | 176943 |         | SER347CYS |

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|                                                          |        |        |           |
|----------------------------------------------------------|--------|--------|-----------|
| Human bek mRNA for fibroblast growth factor receptor-BEK | X52832 | 176943 | SER252TRP |
| Human bek mRNA for fibroblast growth factor receptor-BEK | X52832 | 176943 | PRO253ARG |
| Human bek mRNA for fibroblast growth factor receptor-BEK | X52832 | 176943 | THR341PRO |
| Human bek mRNA for fibroblast growth factor receptor-BEK | X52832 | 176943 | CYS342TRP |
| Human bek mRNA for fibroblast growth factor receptor-BEK | X52832 | 176943 | GLN289PRO |
| Human bek mRNA for fibroblast growth factor receptor-BEK | X52832 | 176943 | TYR375CYS |
| Human bek mRNA for fibroblast growth factor receptor-BEK | X52832 | 176943 | SER372CYS |
| Human bek mRNA for fibroblast growth factor receptor-BEK | X52832 | 176943 | SER252PHE |
| Human bek mRNA for fibroblast growth factor receptor-BEK | X52832 | 176943 | PRO253SER |
| Human bek mRNA for fibroblast growth factor receptor-BEK | X52832 | 176943 | TRP290CYS |
| Human bek mRNA for fibroblast growth factor receptor-BEK | X52832 | 176943 | LYS292GLU |

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|                                                                  |        |        |                |
|------------------------------------------------------------------|--------|--------|----------------|
| fibroblast growth factor<br>receptor-BEK                         | X52832 | 176943 | TRP290ARG      |
| Human bek mRNA for<br>fibroblast growth factor<br>receptor-BEK   | X52832 | 176943 | TRP290GLY      |
| Human bek mRNA for<br>fibroblast growth factor<br>receptor-BEK   | X52832 | 176943 | LYS292GLU      |
| Human bek mRNA for<br>fibroblast growth factor<br>receptor-BEK   | X52832 | 176943 | TRP290ARG      |
| Human bek mRNA for<br>fibroblast growth factor<br>receptor-BEK   | X52832 | 176943 | TRP290GLY      |
| Human bek mRNA for<br>fibroblast growth factor<br>receptor-BEK   | X52832 | 176943 | VAL-VAL<br>DEL |
| Human bek mRNA for<br>fibroblast growth factor<br>receptor-BEK   | X52832 | 176943 | SER351CYS      |
| Human bek mRNA for<br>fibroblast growth factor<br>receptor-BEK   | X52832 | 176943 | SER252PHE      |
| Human beta-LH gene<br>(luteinizing hormone<br>gene beta subunit) | X00264 | 152780 | ILE15THR       |
| Human beta-LH gene<br>(luteinizing hormone                       | X00264 | 152780 | TRP8ARG        |

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| gene beta subunit)                                                | X00264 | 152780 | GLN54ARG                             |
|-------------------------------------------------------------------|--------|--------|--------------------------------------|
| Human beta-LH gene<br>(lutinizizing hormone<br>gene beta subunit) |        |        |                                      |
| Human brain glycogen<br>phosphorylase mRNA,<br>complete cds       | J03544 | 138550 | none found                           |
| Human c-erb-A mRNA<br>for thyroid hormone<br>receptor             | X04707 | 190160 | 1-BP INS, CODON<br>443<br>frameshift |
| Human c-erb-A mRNA<br>for thyroid hormone<br>receptor             | X04707 | 190160 | 1305G-C                              |
| Human c-erb-A mRNA<br>for thyroid hormone<br>receptor             | X04707 | 190160 | C1644i<br>frameshift                 |
| Human c-erb-A mRNA<br>for thyroid hormone<br>receptor             | X04707 | 190160 | EX4-10DEL                            |
| Human c-erb-A mRNA<br>for thyroid hormone<br>receptor             | X04707 | 190160 | HindIII                              |
| Human c-erb-A mRNA<br>for thyroid hormone<br>receptor             | X04707 | 190160 | VAL458ALA                            |
| Human c-erb-A mRNA<br>for thyroid hormone<br>receptor             | X04707 | 190160 | R338L                                |
| Human c-erb-A mRNA<br>for thyroid hormone<br>receptor             | X04707 | 190160 | GLY340ARG                            |

|                                                       |        |        |           |
|-------------------------------------------------------|--------|--------|-----------|
| Human c-erb-A mRNA<br>for thyroid hormone<br>receptor | X04707 | 190160 | ALA229THR |
| Human c-erb-A mRNA<br>for thyroid hormone<br>receptor | X04707 | 190160 | THR332DEL |
| Human c-erb-A mRNA<br>for thyroid hormone<br>receptor | X04707 | 190160 | ARG383HIS |
| Human c-erb-A mRNA<br>for thyroid hormone<br>receptor | X04707 | 190160 | LYS438GLU |
| Human c-erb-A mRNA<br>for thyroid hormone<br>receptor | X04707 | 190160 | GLY340SER |
| Human c-erb-A mRNA<br>for thyroid hormone<br>receptor | X04707 | 190160 | ARG320LEU |
| Human c-erb-A mRNA<br>for thyroid hormone<br>receptor | X04707 | 190160 | ARG311HIS |
| Human c-erb-A mRNA<br>for thyroid hormone<br>receptor | X04707 | 190160 | ARG438HIS |
| Human c-erb-A mRNA<br>for thyroid hormone<br>receptor | X04707 | 190160 | ARG320CYS |
| Human c-erb-A mRNA<br>for thyroid hormone<br>receptor | X04707 | 190160 | ARG338TRP |
| Human c-erb-A mRNA<br>for thyroid hormone<br>receptor | X04707 | 190160 | ALA312THR |

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|                                                       |        |        |           |
|-------------------------------------------------------|--------|--------|-----------|
| for thyroid hormone<br>receptor                       | X04707 | 190160 | GLY327ARG |
| Human c-erb-A mRNA<br>for thyroid hormone<br>receptor | X04707 | 190160 | GLY340VAL |
| Human c-erb-A mRNA<br>for thyroid hormone<br>receptor | X04707 | 190160 | GLY342GLU |
| Human c-erb-A mRNA<br>for thyroid hormone<br>receptor | X04707 | 190160 | MET437VAL |
| Human c-erb-A mRNA<br>for thyroid hormone<br>receptor | X04707 | 190160 | PRO448THR |
| Human c-erb-A mRNA<br>for thyroid hormone<br>receptor | X04707 | 190160 | PRO448HIS |
| Human c-erb-A mRNA<br>for thyroid hormone<br>receptor | X04707 | 190160 | THR337ALA |
| Human c-erb-A mRNA<br>for thyroid hormone<br>receptor | X04707 | 190160 | CYS434TER |
| Human c-erb-A mRNA<br>for thyroid hormone<br>receptor | X04707 | 190160 | CYS446ARG |
| Human c-erb-A mRNA<br>for thyroid hormone<br>receptor | X04707 | 190160 | LEU445HIS |

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|                                                       |        |        |            |
|-------------------------------------------------------|--------|--------|------------|
| receptor<br>Human c-erb-A mRNA<br>for thyroid hormone | X04707 | 190160 | GLY340ASP  |
| receptor<br>Human c-erb-A mRNA<br>for thyroid hormone | X04707 | 190160 | GLN335HIS  |
| receptor<br>Human c-erb-A mRNA<br>for thyroid hormone | X04707 | 190160 | pro453ser  |
| receptor<br>Human c-erb-A mRNA<br>for thyroid hormone | X04707 | 190160 | R316H      |
| receptor<br>Human c-erb-A mRNA<br>for thyroid hormone | X04707 | 190160 | met313thre |
| receptor<br>Human c-erb-A mRNA<br>for thyroid hormone | X04707 | 190160 | L346V      |
| receptor<br>Human c-erb-A mRNA<br>for thyroid hormone | X04707 | 190160 | MET310THR  |
| receptor<br>Human c-erb-A mRNA<br>for thyroid hormone | X04707 | 190160 | LEU325PHE  |
| receptor<br>Human c-erb-A mRNA<br>for thyroid hormone | X04707 | 190160 | ARG243GLN  |
| receptor<br>Human c-erb-A mRNA<br>for thyroid hormone | X04707 | 190160 | ARG243TRP  |

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|                                                                          |        |        |            |
|--------------------------------------------------------------------------|--------|--------|------------|
| Human c-erb-A mRNA<br>for thyroid hormone<br>receptor                    | X04707 | 190160 | ASP317HIS  |
| Human c-erb-A mRNA<br>for thyroid hormone<br>receptor                    | X04707 | 190160 | PHE454CYS  |
| Human c-erb-A mRNA<br>for thyroid hormone<br>receptor                    | X04707 | 190160 | ARG315HIS  |
| Human c-erbA-1<br>mRNA for thyroid<br>hormone receptor alpha             | X55005 | 190120 | LYS370ASN  |
| Human c-erbA-1<br>mRNA for thyroid<br>hormone receptor alpha             | X55005 | 190120 | SER377LEU  |
| Human c-erbA-1<br>mRNA for thyroid<br>hormone receptor alpha             | X55005 | 190120 | SER45ILE   |
| Human cGMP-<br>inhibited cAMP<br>phosphodiesterase<br>mRNA, complete cds | M91667 | 123805 | none found |
| Human colipase<br>mRNA, complete cds                                     | J02883 | 120105 | none found |
| Human collagen type<br>XVIII alpha 1<br>(COL18A1) mRNA,<br>partial cds   | L22548 | 120328 | none found |
| Human CYP11B2 gene<br>for steroid 18-<br>hydroxylase, complete           | D13752 | 124080 | -344C/T    |

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|                                                                       |        |        |          |            |
|-----------------------------------------------------------------------|--------|--------|----------|------------|
| Human CYP11B2 gene<br>for steroid 18-<br>hydroxylase, complete<br>cds | D13752 | 124080 | 5-BP DEL | frameshift |
| Human CYP11B2 gene<br>for steroid 18-<br>hydroxylase, complete<br>cds | D13752 | 124080 | T4986C   |            |
| Human CYP11B2 gene<br>for steroid 18-<br>hydroxylase, complete<br>cds | D13752 | 124080 |          | GLU198ASP  |
| Human CYP11B2 gene<br>for steroid 18-<br>hydroxylase, complete<br>cds | D13752 | 124080 |          | GLU255TER  |
| Human CYP11B2 gene<br>for steroid 18-<br>hydroxylase, complete<br>cds | D13752 | 124080 |          | LYS173ARG  |
| Human CYP11B2 gene<br>for steroid 18-<br>hydroxylase, complete<br>cds | D13752 | 124080 |          | THR185ILE  |
| Human CYP11B2 gene<br>for steroid 18-<br>hydroxylase, complete<br>cds | D13752 | 124080 |          | LEU461PRO  |
| Human CYP11B2 gene<br>for steroid 18-<br>hydroxylase, complete<br>cds | D13752 | 124080 |          | ARG181TRP  |

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|                                                                       |        |        |              |           |
|-----------------------------------------------------------------------|--------|--------|--------------|-----------|
| hydroxylase, complete<br>cds                                          |        |        |              |           |
| Human CYP11B2 gene<br>for steroid 18-<br>hydroxylase, complete<br>cds | D13752 | 124080 |              | VAL386ALA |
| Human CYP11B2 gene<br>for steroid 18-<br>hydroxylase, complete<br>cds | D13752 | 124080 |              | T318M     |
| Human cytochrome<br>P450c21 mRNA, 3' end                              | M17252 | 201910 | 1761Tins     |           |
| Human cytochrome<br>P450c21 mRNA, 3' end                              | M17252 | 201910 | C-G intron 2 |           |
| Human cytochrome<br>P450c21 mRNA, 3' end                              | M17252 | 201910 | DEL          |           |
| Human cytochrome<br>P450c21 mRNA, 3' end                              | M17252 | 201910 | PvuII        |           |
| Human cytochrome<br>P450c21 mRNA, 3' end                              | M17252 | 201910 | TGC to AC    |           |
| Human cytochrome<br>P450c21 mRNA, 3' end                              | M17252 | 201910 | 3-BP INS     | LEU10INS  |
| Human cytochrome<br>P450c21 mRNA, 3' end                              | M17252 | 201910 | 656 A-->G    |           |
| Human cytochrome<br>P450c21 mRNA, 3' end                              | M17252 | 201910 | 8-BP DEL     |           |
| Human cytochrome<br>P450c21 mRNA, 3' end                              | M17252 | 201910 | ClusterE6    |           |
| Human cytochrome<br>P450c21 mRNA, 3' end                              | M17252 | 201910 | F306+t       |           |
| Human cytochrome<br>P450c21 mRNA, 3' end                              | M17252 | 201910 | G-T exon 7   |           |

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|                      |        |        |                                      |           |
|----------------------|--------|--------|--------------------------------------|-----------|
| P450c21 mRNA, 3' end | M17252 | 201910 | GG dinucleotide to a<br>C in exon 10 |           |
| Human cytochrome     |        |        | HaeIII                               |           |
| P450c21 mRNA, 3' end | M17252 | 201910 |                                      |           |
| Human cytochrome     |        |        |                                      |           |
| P450c21 mRNA, 3' end | M17252 | 201910 | IVS2AS A/C-G, -13                    |           |
| Human cytochrome     |        |        |                                      |           |
| P450c21 mRNA, 3' end | M17252 | 201910 | IVS7DS, G-C, +1                      |           |
| Human cytochrome     |        |        |                                      |           |
| P450c21 mRNA, 3' end | M17252 | 201910 | NcoI                                 |           |
| Human cytochrome     |        |        |                                      |           |
| P450c21 mRNA, 3' end | M17252 | 201910 | Rsa I                                |           |
| Human cytochrome     |        |        |                                      |           |
| P450c21 mRNA, 3' end | M17252 | 201910 | T-A exon 4                           |           |
| Human cytochrome     |        |        |                                      | ILE172ASN |
| P450c21 mRNA, 3' end | M17252 | 201910 |                                      | VAL281LEU |
| Human cytochrome     |        |        |                                      | PRO30LEU  |
| P450c21 mRNA, 3' end | M17252 | 201910 |                                      | SER268THR |
| Human cytochrome     |        |        |                                      | GLY292SER |
| P450c21 mRNA, 3' end | M17252 | 201910 |                                      | PRO453SER |
| Human cytochrome     |        |        |                                      | TYR102ARG |
| P450c21 mRNA, 3' end | M17252 | 201910 |                                      | ILE235ASN |
| Human cytochrome     |        |        |                                      |           |
| P450c21 mRNA, 3' end | M17252 | 201910 |                                      |           |

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|                                          |        |        |           |
|------------------------------------------|--------|--------|-----------|
| Human cytochrome<br>P450c21 mRNA, 3' end | M17252 | 201910 | VAL236GLU |
| Human cytochrome<br>P450c21 mRNA, 3' end | M17252 | 201910 | MET238LYS |
| Human cytochrome<br>P450c21 mRNA, 3' end | M17252 | 201910 | GLN318TER |
| Human cytochrome<br>P450c21 mRNA, 3' end | M17252 | 201910 | ARG339HIS |
| Human cytochrome<br>P450c21 mRNA, 3' end | M17252 | 201910 | TRP406TER |
| Human cytochrome<br>P450c21 mRNA, 3' end | M17252 | 201910 | GLU380ASP |
| Human cytochrome<br>P450c21 mRNA, 3' end | M17252 | 201910 | Q318X     |
| Human cytochrome<br>P450c21 mRNA, 3' end | M17252 | 201910 | R356W     |
| Human cytochrome<br>P450c21 mRNA, 3' end | M17252 | 201910 | I236N     |
| Human cytochrome<br>P450c21 mRNA, 3' end | M17252 | 201910 | V237E     |
| Human cytochrome<br>P450c21 mRNA, 3' end | M17252 | 201910 | M239K     |
| Human cytochrome<br>P450c21 mRNA, 3' end | M17252 | 201910 | GLY524SER |
| Human cytochrome<br>P450c21 mRNA, 3' end | M17252 | 201910 | R356Q     |
| Human cytochrome<br>P450c21 mRNA, 3' end | M17252 | 201910 | Y97X      |
| Human cytochrome<br>P450c21 mRNA, 3' end | M17252 | 201910 | Arg357Trp |
| Human cytochrome<br>P450c21 mRNA, 3' end | M17252 | 201910 | D183E     |

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|                                                                                                                |        |        |                        |
|----------------------------------------------------------------------------------------------------------------|--------|--------|------------------------|
| P450c21 mRNA, 3' end                                                                                           | M17252 | 201910 | W23X                   |
| Human cytochrome                                                                                               |        |        |                        |
| P450c21 mRNA, 3' end                                                                                           | U26644 | 600212 | none found             |
| Human fatty acid<br>synthase (fas) mRNA,<br>complete cds                                                       | X52560 | 189965 | none found             |
| Human gene for<br>nuclear factor NF-IL6                                                                        | U01157 | 138032 | none found             |
| Human glucagon-like<br>peptide-1 receptor<br>mRNA with CA<br>dinucleotide repeat,<br>complete cds              | M32977 | 192240 | none found             |
| Human heparin-<br>binding vascular<br>endothelial growth<br>factor (VEGF) mRNA,<br>complete cds                | J03540 | 151670 | SER267PHE              |
| Human hepatic lipase<br>mRNA, complete cds                                                                     | J03540 | 151670 | THR383MET              |
| Human hepatic lipase<br>mRNA, complete cds                                                                     | M57732 | 142410 | A-C, -58               |
| Human hepatic nuclear<br>factor 1 (TCF1)<br>mRNA, complete cds,<br>clones HCL10,<br>HCL12, HCL17, and<br>HCL20 | M57732 | 142410 | 1-BP DEL<br>frameshift |
| Human hepatic nuclear<br>factor 1 (TCF1)<br>mRNA, complete cds,                                                |        |        |                        |

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|                                                                                                                |        |        |               |            |
|----------------------------------------------------------------------------------------------------------------|--------|--------|---------------|------------|
| clones HCL10,<br>HCL12, HCL17, and<br>HCL20                                                                    | M57732 | 142410 | 1-BP INS      | frameshift |
| Human hepatic nuclear<br>factor 1 (TCF1)<br>mRNA, complete cds,<br>clones HCL10,<br>HCL12, HCL17, and<br>HCL20 | M57732 | 142410 | RsaI promoter |            |
| Human hepatic nuclear<br>factor 1 (TCF1)<br>mRNA, complete cds,<br>clones HCL10,<br>HCL12, HCL17, and<br>HCL20 | M57732 | 142410 |               | PRO447LEU  |
| Human hepatic nuclear<br>factor 1 (TCF1)<br>mRNA, complete cds,<br>clones HCL10,<br>HCL12, HCL17, and<br>HCL20 | M57732 | 142410 |               | E619K      |
| Human hepatic nuclear<br>factor 1 (TCF1)<br>mRNA, complete cds,<br>clones HCL10,<br>HCL12, HCL17, and<br>HCL20 | M57732 | 142410 |               | R537T      |

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|                                                                                                                |        |        |           |
|----------------------------------------------------------------------------------------------------------------|--------|--------|-----------|
| HCL12, HCL17, and<br>HCL20                                                                                     | M57732 | 142410 | Ala/Val98 |
| Human hepatic nuclear<br>factor 1 (TCF1)<br>mRNA, complete cds,<br>clones HCL10,<br>HCL12, HCL17, and<br>HCL20 |        |        |           |
| Human hepatic nuclear<br>factor 1 (TCF1)<br>mRNA, complete cds,<br>clones HCL10,<br>HCL12, HCL17, and<br>HCL20 | M57732 | 142410 | TYR122CYS |
| Human hepatic nuclear<br>factor 1 (TCF1)<br>mRNA, complete cds,<br>clones HCL10,<br>HCL12, HCL17, and<br>HCL20 | M57732 | 142410 | THR620ILE |
| Human hepatic nuclear<br>factor 1 (TCF1)<br>mRNA, complete cds,<br>clones HCL10,<br>HCL12, HCL17, and<br>HCL20 | M57732 | 142410 | Gly574Ser |
| Human hepatic nuclear<br>factor 1 (TCF1)<br>mRNA, complete cds,<br>clones HCL10,<br>HCL12, HCL17, and<br>HCL20 | M57732 | 142410 | Cys241Gly |



|                                                                                                                         |        |        |              |
|-------------------------------------------------------------------------------------------------------------------------|--------|--------|--------------|
| HCL20<br>Human hepatic nuclear<br>factor 1 (TCF1)<br>mRNA, complete cds,<br>clones HCL10,<br>HCL12, HCL17, and<br>HCL20 | M57732 | 142410 | Glu48Lys     |
| HCL20<br>Human hepatic nuclear<br>factor 1 (TCF1)<br>mRNA, complete cds,<br>clones HCL10,<br>HCL12, HCL17, and<br>HCL20 | M57732 | 142410 | Pro291fsdelA |
| HCL20<br>Human hepatic nuclear<br>factor 1 (TCF1)<br>mRNA, complete cds,<br>clones HCL10,<br>HCL12, HCL17, and<br>HCL20 | M57732 | 142410 | ARG272HIS    |
| HCL20<br>Human hepatic nuclear<br>factor 1 (TCF1)<br>mRNA, complete cds,<br>clones HCL10,<br>HCL12, HCL17, and<br>HCL20 | M57732 | 142410 | ARG583GLY    |
| HCL20<br>Human hepatic nuclear<br>factor 1 (TCF1)<br>mRNA, complete cds,<br>clones HCL10,<br>HCL12, HCL17, and<br>HCL20 | M57732 | 142410 | K205Q        |

|                                                                                                 |        |        |                     |
|-------------------------------------------------------------------------------------------------|--------|--------|---------------------|
| Human hepatic nuclear factor 1 (TCF1) mRNA, complete cds, clones HCL10, HCL12, HCL17, and HCL20 | M57732 | 142410 | R131Q               |
| Human hepatic nuclear factor 1 (TCF1) mRNA, complete cds, clones HCL10, HCL12, HCL17, and HCL20 | M57732 | 142410 | T392fsdelA          |
| Human hepatic nuclear factor 1 (TCF1) mRNA, complete cds, clones HCL10, HCL12, HCL17, and HCL20 | M57732 | 142410 | L12H                |
| Human hepatic nuclear factor 1 (TCF1) mRNA, complete cds, clones HCL10, HCL12, HCL17, and HCL20 | M57732 | 142410 | L584S585fsinsT<br>C |
| Human hepatic nuclear factor 1 (TCF1) mRNA, complete cds, clones HCL10, HCL12, HCL17, and HCL20 | M57732 | 142410 | P379fsdelCT         |
| Human hepatic nuclear factor 1 (TCF1) mRNA, complete cds, clones HCL10, HCL12, HCL17, and HCL20 | M57732 | 142410 | R263C               |

|                                                                                                                |        |        |            |
|----------------------------------------------------------------------------------------------------------------|--------|--------|------------|
| factor 1 (TCF1)<br>mRNA, complete cds,<br>clones HCL10,<br>HCL12, HCL17, and<br>HCL20                          | M57732 | 142410 | G191D      |
| Human hepatic nuclear<br>factor 1 (TCF1)<br>mRNA, complete cds,<br>clones HCL10,<br>HCL12, HCL17, and<br>HCL20 | M57732 | 142410 | GLY319SER  |
| Human hepatic nuclear<br>factor 1 (TCF1)<br>mRNA, complete cds,<br>clones HCL10,<br>HCL12, HCL17, and<br>HCL20 | U39840 | 602294 | none found |
| Human hormone-<br>sensitive lipase<br>testicular isoform<br>mRNA, complete cds                                 | U40002 | 151750 | Arg309Cys  |
| Human hormone-<br>sensitive lipase<br>testicular isoform<br>mRNA, complete cds                                 | D83260 | 601125 | none found |

|                                                                                   |        |        |                  |                |
|-----------------------------------------------------------------------------------|--------|--------|------------------|----------------|
| Human insulin<br>promoter factor 1<br>(IPF1) mRNA,<br>complete cds                | U30329 | 600733 | 1-BP DEL         | frameshift     |
| Human insulin-<br>degrading enzyme<br>(IDE) mRNA,<br>complete cds                 | M21188 | 146680 | none found       |                |
| Human insulin-<br>responsive glucose<br>transporter (GLUT4)<br>mRNA, complete cds | M20747 | 138190 |                  | VAL383ILE      |
| Human liver glycogen<br>phosphorylase type IV<br>mRNA, 3' end                     | M36807 | 232700 | IVS13DS, G-A, +1 |                |
| Human liver glycogen<br>phosphorylase type IV<br>mRNA, 3' end                     | M36807 | 232700 | IVS14DS, G-A, +1 |                |
| Human liver glycogen<br>phosphorylase type IV<br>mRNA, 3' end                     | M36807 | 232700 | IVS4AS, G-C, -1  |                |
| Human liver glycogen<br>phosphorylase type IV<br>mRNA, 3' end                     | M36807 | 232700 |                  | ASN338SER      |
| Human liver glycogen<br>phosphorylase type IV<br>mRNA, 3' end                     | M36807 | 232700 |                  | ASN376LYS      |
| Human liver glycogen<br>phosphorylase type IV<br>mRNA, 3' end                     | M36807 | 232700 |                  | VAL221ILE      |
| Human long-chain                                                                  | L09229 | 152425 | A-->T            | new initiation |

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|                                                                                       |        |        |                             |                          |
|---------------------------------------------------------------------------------------|--------|--------|-----------------------------|--------------------------|
| acyl-coenzyme A<br>synthetase (FACL1)<br>mRNA, complete cds                           |        |        |                             | codon +18<br>amino acids |
| Human luteinizing<br>hormone-<br>choriogonadotropin<br>receptor mRNA,<br>complete cds | M63108 | 152790 | 6-BP DEL, NT1822            |                          |
| Human luteinizing<br>hormone-<br>choriogonadotropin<br>receptor mRNA,<br>complete cds | M63108 | 152790 | LEU-GLN INS,<br>CODON 19-20 |                          |
| Human luteinizing<br>hormone-<br>choriogonadotropin<br>receptor mRNA,<br>complete cds | M63108 | 152790 |                             | SER616TYR                |
| Human luteinizing<br>hormone-<br>choriogonadotropin<br>receptor mRNA,<br>complete cds | M63108 | 152790 |                             | ARG554TER                |
| Human luteinizing<br>hormone-<br>choriogonadotropin<br>receptor mRNA,<br>complete cds | M63108 | 152790 |                             | ALA593PRO                |
| Human luteinizing<br>hormone-<br>choriogonadotropin<br>receptor mRNA,<br>complete cds | M63108 | 152790 |                             | ASP578GLY                |

|                                                                                                                         |        |        |           |
|-------------------------------------------------------------------------------------------------------------------------|--------|--------|-----------|
| receptor mRNA,<br>complete cds<br>Human luteinizing<br>hormone-<br>choriogonadotropin<br>receptor mRNA,<br>complete cds | M63108 | 152790 | ILE625LYS |
| Human luteinizing<br>hormone-<br>choriogonadotropin<br>receptor mRNA,<br>complete cds                                   | M63108 | 152790 | ILE542LEU |
| Human luteinizing<br>hormone-<br>choriogonadotropin<br>receptor mRNA,<br>complete cds                                   | M63108 | 152790 | ALA373VAL |
| Human luteinizing<br>hormone-<br>choriogonadotropin<br>receptor mRNA,<br>complete cds                                   | M63108 | 152790 | GLU354LYS |
| Human luteinizing<br>hormone-<br>choriogonadotropin<br>receptor mRNA,<br>complete cds                                   | M63108 | 152790 | ARG133CYS |
| Human luteinizing<br>hormone-<br>choriogonadotropin<br>receptor mRNA,<br>complete cds                                   | M63108 | 152790 | ASP578GLY |

|                                                                                                    |        |        |           |
|----------------------------------------------------------------------------------------------------|--------|--------|-----------|
| complete cds<br>Human luteinizing hormone-<br>choriogonadotropin<br>receptor mRNA,<br>complete cds | M63108 | 152790 | ALA572VAL |
| Human luteinizing hormone-<br>choriogonadotropin<br>receptor mRNA,<br>complete cds                 | M63108 | 152790 | THR577ILE |
| Human luteinizing hormone-<br>choriogonadotropin<br>receptor mRNA,<br>complete cds                 | M63108 | 152790 | ASP582GLY |
| Human luteinizing hormone-<br>choriogonadotropin<br>receptor mRNA,<br>complete cds                 | M63108 | 152790 | MET575ILE |
| Human luteinizing hormone-<br>choriogonadotropin<br>receptor mRNA,<br>complete cds                 | M63108 | 152790 | MET398THR |
| Human luteinizing hormone-<br>choriogonadotropin<br>receptor mRNA,<br>complete cds                 | M63108 | 152790 | CYS545TER |

|                                                                     |        |        |                 |            |
|---------------------------------------------------------------------|--------|--------|-----------------|------------|
| Human<br>metalloendopeptidase<br>homolog (PEX)<br>mRNA, partial cds | U60475 | 307800 | 2-BP DEL        | frameshift |
| Human<br>metalloendopeptidase<br>homolog (PEX)<br>mRNA, partial cds | U60475 | 307800 | A-G, NT-429     |            |
| Human<br>metalloendopeptidase<br>homolog (PEX)<br>mRNA, partial cds | U60475 | 307800 | IVS1AS, G-A, -1 |            |
| Human<br>metalloendopeptidase<br>homolog (PEX)<br>mRNA, partial cds | U60475 | 307800 | IVS1AS, G-C, -1 |            |
| Human<br>metalloendopeptidase<br>homolog (PEX)<br>mRNA, partial cds | U60475 | 307800 |                 | LEU555PRO  |
| Human<br>metalloendopeptidase<br>homolog (PEX)<br>mRNA, partial cds | U60475 | 307800 |                 | CYS82TYR   |
| Human<br>metalloendopeptidase<br>homolog (PEX)<br>mRNA, partial cds | U60475 | 307800 |                 | LEU274TER  |
| Human<br>metalloendopeptidase<br>homolog (PEX)                      | U60475 | 307800 |                 | MET250ILE  |



|                                                                              |        |        |                 |            |
|------------------------------------------------------------------------------|--------|--------|-----------------|------------|
| mRNA, partial cds<br>Human<br>metalloendopeptidase<br>homolog (PEX)          | U60475 | 307800 |                 | PHE249SER  |
| mRNA, partial cds<br>Human molecular<br>marker (EPC-1) gene,<br>complete cds | M90439 | 172860 | G to A 5        |            |
| Human molecular<br>marker (EPC-1) gene,<br>complete cds                      | M90439 | 172860 |                 | Met72Thr   |
| Human molecular<br>marker (EPC-1) gene,<br>complete cds                      | M90439 | 172860 |                 | Thr130Thr  |
| Human molecular<br>marker (EPC-1) gene,<br>complete cds                      | M90439 | 172860 |                 | Tyr321Tyr  |
| Human mRNA for<br>alpha-tocopherol<br>transfer protein,<br>complete cds      | D49488 | 600415 | 1-BP DEL 744    |            |
| Human mRNA for<br>alpha-tocopherol<br>transfer protein,<br>complete cds      | D49488 | 600415 | 1-BP DEL, 485T  | frameshift |
| Human mRNA for<br>alpha-tocopherol<br>transfer protein,<br>complete cds      | D49488 | 600415 | 2-BP INS, 513TT |            |
| Human mRNA for<br>alpha-tocopherol<br>transfer protein,<br>complete cds      | D49488 | 600415 | 552G-A          |            |

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|                                                                         |        |        |                                      |
|-------------------------------------------------------------------------|--------|--------|--------------------------------------|
| transfer protein,<br>complete cds                                       | D49488 | 600415 | HIS101GLN                            |
| Human mRNA for<br>alpha-tocopherol<br>transfer protein,<br>complete cds | D49488 | 600415 | ARG192HIS                            |
| Human mRNA for<br>alpha-tocopherol<br>transfer protein,<br>complete cds | D49488 | 600415 | ARG134TER                            |
| Human mRNA for<br>carboxypeptidase E<br>(EC 3.4.17.10)                  | X51405 | 114855 | none found                           |
| Human mRNA for<br>cytochrome P-450 (11<br>Beta)                         | X55764 | 202010 | 2-BP INS, CODON<br>394<br>frameshift |
| Human mRNA for<br>cytochrome P-450 (11<br>Beta)                         | X55764 | 202010 | 28bp deletion                        |
| Human mRNA for<br>cytochrome P-450 (11<br>Beta)                         | X55764 | 202010 | 5 bp duplication                     |
| Human mRNA for<br>cytochrome P-450 (11<br>Beta)                         | X55764 | 202010 | CHIMERA                              |
| Human mRNA for<br>cytochrome P-450 (11<br>Beta)                         | X55764 | 202010 | MspI                                 |

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|                                                 |        |        |       |           |
|-------------------------------------------------|--------|--------|-------|-----------|
| Beta)<br>Human mRNA for<br>cytochrome P-450 (11 | X55764 | 202010 | PvuII |           |
| Beta)<br>Human mRNA for<br>cytochrome P-450 (11 | X55764 | 202010 |       | ARG448HIS |
| Beta)<br>Human mRNA for<br>cytochrome P-450 (11 | X55764 | 202010 |       | TRP116TER |
| Beta)<br>Human mRNA for<br>cytochrome P-450 (11 | X55764 | 202010 |       | N133H     |
| Beta)<br>Human mRNA for<br>cytochrome P-450 (11 | X55764 | 202010 |       | P42S      |
| Beta)<br>Human mRNA for<br>cytochrome P-450 (11 | X55764 | 202010 |       | Y423X     |
| Beta)<br>Human mRNA for<br>cytochrome P-450 (11 | X55764 | 202010 |       | arg384gly |
| Beta)<br>Human mRNA for<br>cytochrome P-450 (11 | X55764 | 202010 |       | ARG374GLN |
| Beta)<br>Human mRNA for<br>cytochrome P-450 (11 | X55764 | 202010 |       | THR318MET |
| Beta)<br>Human mRNA for<br>cytochrome P-450 (11 | X55764 | 202010 |       | C494F     |

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|---------------------------------------------------------------------------------------------------------------------------------|--------|--------|-----------------------------------|-----------|
| Human mRNA for<br>cytochrome P-450 (11<br>Beta)                                                                                 | X55764 | 202010 |                                   | G267D     |
| Human mRNA for<br>cytochrome P-450 (11<br>Beta)                                                                                 | X55764 | 202010 |                                   | G267R     |
| Human mRNA for<br>cytochrome P-450 (11<br>Beta)                                                                                 | X55764 | 202010 |                                   | Q356X     |
| Human mRNA for<br>cytochrome P-450 (11<br>Beta)                                                                                 | X55764 | 202010 |                                   | R427H     |
| Human mRNA for<br>glioblastoma-derived<br>T-cell suppressor factor<br>G-TsF (transforming<br>growth factor-beta2,<br>TGF-beta2) | Y00083 | 190220 | none found                        |           |
| Human mRNA for<br>plasminogen                                                                                                   | X05199 | 173350 | IVS17, 1-BP DEL,<br>G, +1<br>TaqI |           |
| Human mRNA for<br>plasminogen                                                                                                   | X05199 | 173350 |                                   | GLU460TER |
| Human mRNA for<br>plasminogen                                                                                                   | X05199 | 173350 |                                   | ALA600THR |
| Human mRNA for<br>plasminogen                                                                                                   | X05199 | 173350 |                                   | ARG216HIS |
| Human mRNA for<br>plasminogen                                                                                                   | X05199 | 173350 |                                   | GLY732ARG |
| Human mRNA for<br>plasminogen                                                                                                   | X05199 | 173350 |                                   | LYS19GLU  |

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|                                                               |        |        |                  |
|---------------------------------------------------------------|--------|--------|------------------|
| Human plasminogen mRNA for plasminogen                        | X05199 | 173350 | LYS212DEL        |
| Human mRNA for plasminogen                                    | X05199 | 173350 | SER572PRO        |
| Human mRNA for plasminogen                                    | X05199 | 173350 | TRP597TER        |
| Human mRNA for plasminogen                                    | X05199 | 173350 | VAL355PHE        |
| Human mRNA for plasminogen                                    | X05199 | 173350 | D676N            |
| Human mRNA for plasminogen                                    | X05199 | 173350 | Ala675Thr        |
| Human mRNA for transforming growth factor-beta (TGF-beta)     | X02812 | 190180 | 713-8delC        |
| Human mRNA for transforming growth factor-beta (TGF-beta)     | X02812 | 190180 | Leu10-->Pro      |
| Human mRNA for transforming growth factor-beta (TGF-beta)     | X02812 | 190180 | Arg25-->Pro      |
| Human mRNA for transforming growth factor-beta 3 (TGF-beta 3) | X14149 | 190230 | none found       |
| Human mRNA for variant hepatic nuclear factor 1 (vHNF1)       | X58840 | 189907 | 75-BP DEL, NT409 |
| Human mRNA for variant hepatic nuclear                        | X58840 | 189907 | ARG177TER        |

|                                                                                                                             |        |        |            |           |
|-----------------------------------------------------------------------------------------------------------------------------|--------|--------|------------|-----------|
| factor 1 (vHNF1)                                                                                                            |        |        |            |           |
| Human mRNA<br>fragment for second<br>calcitonin gene related<br>peptide (CGRP) from<br>medullary thyroid<br>carcinoma (MTC) | X02404 | 114160 | none found |           |
| Human mRNA for<br>pro-cathepsin L (major<br>excreted protein MEP)                                                           | X12451 | 116880 | none found |           |
| Human muscle<br>glycogen synthase<br>mRNA, complete cds                                                                     | J04501 | 138570 | TTC342TTT  |           |
| Human muscle<br>glycogen synthase<br>mRNA, complete cds                                                                     | J04501 | 138570 |            | Gln71His  |
| Human muscle<br>glycogen synthase<br>mRNA, complete cds                                                                     | J04501 | 138570 |            | Gly464Ser |
| Human muscle<br>glycogen synthase<br>mRNA, complete cds                                                                     | J04501 | 138570 |            | Met416Val |
| Human myeloid-<br>specific C/EBP-epsilon<br>transcription factor<br>(CEBPE) gene,<br>complete cds                           | U80982 | 600749 | none found |           |
| Human neurokinin A<br>receptor (NK-2R)<br>mRNA, complete cds                                                                | M57414 | 162321 | none found |           |
| Human NF-IL6-beta                                                                                                           | M83667 | 116898 | none found |           |

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|                                                                 |        |        |                                         |             |
|-----------------------------------------------------------------|--------|--------|-----------------------------------------|-------------|
| protein mRNA,<br>complete cds                                   |        |        |                                         |             |
| Human obese (ob)<br>mRNA, complete cds                          | U18915 | 164160 | -1387 G/A                               |             |
| Human obese (ob)<br>mRNA, complete cds                          | U18915 | 164160 | 1-BP DEL                                | frameshift  |
| Human obese (ob)<br>mRNA, complete cds                          | U18915 | 164160 | A --> G + 19 exon1                      |             |
| Human obese (ob)<br>mRNA, complete cds                          | U18915 | 164160 | C(-188)A                                |             |
| Human obese (ob)<br>mRNA, complete cds                          | U18915 | 164160 |                                         | ARG105TRP   |
| Human obese (ob)<br>mRNA, complete cds                          | U18915 | 164160 |                                         | Glu-126-Gln |
| Human obese (ob)<br>mRNA, complete cds                          | U18915 | 164160 |                                         | Ser-91-Ser  |
| Human pancreatic<br>beta-cell glucokinase<br>mRNA, complete cds | M88011 | 138079 | CCC[Pro]--<br>>CCG[Pro] at codon<br>145 |             |
| Human pancreatic<br>beta-cell glucokinase<br>mRNA, complete cds | M88011 | 138079 | intron 1 a variant<br>(C-->T)           |             |
| Human pancreatic<br>beta-cell glucokinase<br>mRNA, complete cds | M88011 | 138079 | (-258) G-to-A                           |             |
| Human pancreatic<br>beta-cell glucokinase<br>mRNA, complete cds | M88011 | 138079 | (TAC-->TAT) in<br>codon 215             |             |
| Human pancreatic<br>beta-cell glucokinase<br>mRNA, complete cds | M88011 | 138079 | -120 (G-->T)                            |             |

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|-----------------------------------------------------------------|--------|--------|---------------------------------------------------------------------|
| Human pancreatic<br>beta-cell glucokinase<br>mRNA, complete cds | M88011 | 138079 | -194 (A-->G)                                                        |
| Human pancreatic<br>beta-cell glucokinase<br>mRNA, complete cds | M88011 | 138079 | -282 (C-->T)                                                        |
| Human pancreatic<br>beta-cell glucokinase<br>mRNA, complete cds | M88011 | 138079 | -30 G/A                                                             |
| Human pancreatic<br>beta-cell glucokinase<br>mRNA, complete cds | M88011 | 138079 | 10-bp (base pair)<br>deletion in exon 3;                            |
| Human pancreatic<br>beta-cell glucokinase<br>mRNA, complete cds | M88011 | 138079 | 33-bp deletion at the<br>exon 5/intron 5<br>junction<br>403 (C-->G) |
| Human pancreatic<br>beta-cell glucokinase<br>mRNA, complete cds | M88011 | 138079 | 603 (G-->T)                                                         |
| Human pancreatic<br>beta-cell glucokinase<br>mRNA, complete cds | M88011 | 138079 | A--> G 244                                                          |
| Human pancreatic<br>beta-cell glucokinase<br>mRNA, complete cds | M88011 | 138079 | C--> T 8 bp 3' to the<br>exon 9                                     |
| Human pancreatic<br>beta-cell glucokinase<br>mRNA, complete cds | M88011 | 138079 | compound imperfect<br>dinucleotide repeat                           |
| Human pancreatic<br>beta-cell glucokinase<br>mRNA, complete cds | M88011 | 138079 | G--> A 13                                                           |

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|-----------------------------------------------------------------|--------|--------|----------------------|-----------|
| beta-cell glucokinase<br>mRNA, complete cds                     | M88011 | 138079 | IVS4DS, 15-BP<br>DEL |           |
| Human pancreatic<br>beta-cell glucokinase<br>mRNA, complete cds | M88011 | 138079 | TGG257-->CGG257      |           |
| Human pancreatic<br>beta-cell glucokinase<br>mRNA, complete cds | M88011 | 138079 |                      | ARG186TER |
| Human pancreatic<br>beta-cell glucokinase<br>mRNA, complete cds | M88011 | 138079 |                      | GLU265TER |
| Human pancreatic<br>beta-cell glucokinase<br>mRNA, complete cds | M88011 | 138079 |                      | GLU279TER |
| Human pancreatic<br>beta-cell glucokinase<br>mRNA, complete cds | M88011 | 138079 |                      | GLY261ARG |
| Human pancreatic<br>beta-cell glucokinase<br>mRNA, complete cds | M88011 | 138079 |                      | GLY299ARG |
| Human pancreatic<br>beta-cell glucokinase<br>mRNA, complete cds | M88011 | 138079 |                      | SER131PRO |
| Human pancreatic<br>beta-cell glucokinase<br>mRNA, complete cds | M88011 | 138079 |                      | THR228MET |
| Human pancreatic<br>beta-cell glucokinase<br>mRNA, complete cds | M88011 | 138079 |                      | VAL455MET |

|                       |        |        |  |               |
|-----------------------|--------|--------|--|---------------|
| mRNA, complete cds    |        |        |  |               |
| Human pancreatic      | M88011 | 138079 |  | Val62Ala      |
| beta-cell glucokinase |        |        |  |               |
| mRNA, complete cds    |        |        |  |               |
| Human pancreatic      | M88011 | 138079 |  | Thr209--      |
| beta-cell glucokinase |        |        |  | >Met209       |
| mRNA, complete cds    |        |        |  |               |
| Human pancreatic      | M88011 | 138079 |  | Gly261--      |
| beta-cell glucokinase |        |        |  | >Glu261       |
| mRNA, complete cds    |        |        |  |               |
| Human pancreatic      | M88011 | 138079 |  | Arg36-->Trp36 |
| beta-cell glucokinase |        |        |  |               |
| mRNA, complete cds    |        |        |  |               |
| Human pancreatic      | M88011 | 138079 |  | Glu70-->Lys   |
| beta-cell glucokinase |        |        |  |               |
| mRNA, complete cds    |        |        |  |               |
| Human pancreatic      | M88011 | 138079 |  | Ser131-->Pro  |
| beta-cell glucokinase |        |        |  |               |
| mRNA, complete cds    |        |        |  |               |
| Human pancreatic      | M88011 | 138079 |  | Ala188-->Thr  |
| beta-cell glucokinase |        |        |  |               |
| mRNA, complete cds    |        |        |  |               |
| Human pancreatic      | M88011 | 138079 |  | Trp257-->Arg  |
| beta-cell glucokinase |        |        |  |               |
| mRNA, complete cds    |        |        |  |               |
| Human pancreatic      | M88011 | 138079 |  | Lys414-->Glu  |
| beta-cell glucokinase |        |        |  |               |
| mRNA, complete cds    |        |        |  |               |
| Human pancreatic      | M88011 | 138079 |  | Asp4-->Asn    |
| beta-cell glucokinase |        |        |  |               |
| mRNA, complete cds    |        |        |  |               |

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|-----------------------------------------------------------------------------|--------|--------|-----------------------|
| Human pancreatic<br>beta-cell glucokinase<br>mRNA, complete cds             | M88011 | 138079 | Ala11Thr              |
| Human parathyroid cell<br>calcium-sensing<br>receptor mRNA,<br>complete cds | U20759 | 601199 | (CA)n                 |
| Human parathyroid cell<br>calcium-sensing<br>receptor mRNA,<br>complete cds | U20759 | 601199 | 2-BP DEL/1-BP INS     |
| Human parathyroid cell<br>calcium-sensing<br>receptor mRNA,<br>complete cds | U20759 | 601199 | ALU INS, CODON<br>877 |
| Human parathyroid cell<br>calcium-sensing<br>receptor mRNA,<br>complete cds | U20759 | 601199 | T/C fifth intron      |
| Human parathyroid cell<br>calcium-sensing<br>receptor mRNA,<br>complete cds | U20759 | 601199 | ARG796TRP             |
| Human parathyroid cell<br>calcium-sensing<br>receptor mRNA,<br>complete cds | U20759 | 601199 | GLU298LYS             |
| Human parathyroid cell<br>calcium-sensing<br>receptor mRNA,<br>complete cds | U20759 | 601199 | ARG185GLN             |

|                                                                             |        |        |           |
|-----------------------------------------------------------------------------|--------|--------|-----------|
| Human parathyroid cell<br>calcium-sensing<br>receptor mRNA,<br>complete cds | U20759 | 601199 | GLU128ALA |
| Human parathyroid cell<br>calcium-sensing<br>receptor mRNA,<br>complete cds | U20759 | 601199 | ARG227LEU |
| Human parathyroid cell<br>calcium-sensing<br>receptor mRNA,<br>complete cds | U20759 | 601199 | CYS582TYR |
| Human parathyroid cell<br>calcium-sensing<br>receptor mRNA,<br>complete cds | U20759 | 601199 | GLU681HIS |
| Human parathyroid cell<br>calcium-sensing<br>receptor mRNA,<br>complete cds | U20759 | 601199 | ALA116THR |
| Human parathyroid cell<br>calcium-sensing<br>receptor mRNA,<br>complete cds | U20759 | 601199 | PHE806SER |
| Human parathyroid cell<br>calcium-sensing<br>receptor mRNA,<br>complete cds | U20759 | 601199 | THR151MET |
| Human parathyroid cell<br>calcium-sensing<br>receptor mRNA,                 | U20759 | 601199 | ASN118LYS |

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|                                                                                             |        |        |           |
|---------------------------------------------------------------------------------------------|--------|--------|-----------|
| complete cds<br>Human parathyroid cell<br>calcium-sensing<br>receptor mRNA,<br>complete cds | U20759 | 601199 | PHE128LEU |
| Human parathyroid cell<br>calcium-sensing<br>receptor mRNA,<br>complete cds                 | U20759 | 601199 | THR151MET |
| Human parathyroid cell<br>calcium-sensing<br>receptor mRNA,<br>complete cds                 | U20759 | 601199 | GLU191LYS |
| Human parathyroid cell<br>calcium-sensing<br>receptor mRNA,<br>complete cds                 | U20759 | 601199 | PHE612SER |
| Human parathyroid cell<br>calcium-sensing<br>receptor mRNA,<br>complete cds                 | U20759 | 601199 | LEU773ARG |
| Human parathyroid cell<br>calcium-sensing<br>receptor mRNA,<br>complete cds                 | U20759 | 601199 | ARG185TER |
| Human parathyroid cell<br>calcium-sensing<br>receptor mRNA,<br>complete cds                 | U20759 | 601199 | GLY670GLU |
| Human parathyroid cell<br>calcium-sensing<br>receptor mRNA,<br>complete cds                 | U20759 | 601199 | PRO40ALA  |

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|                                                                             |        |        |           |
|-----------------------------------------------------------------------------|--------|--------|-----------|
| receptor mRNA,<br>complete cds                                              | U20759 | 601199 | ARG228GLN |
| Human parathyroid cell<br>calcium-sensing<br>receptor mRNA,<br>complete cds | U20759 | 601199 | THR139MET |
| Human parathyroid cell<br>calcium-sensing<br>receptor mRNA,<br>complete cds | U20759 | 601199 | GLY144GLU |
| Human parathyroid cell<br>calcium-sensing<br>receptor mRNA,<br>complete cds | U20759 | 601199 | ARG63MET  |
| Human parathyroid cell<br>calcium-sensing<br>receptor mRNA,<br>complete cds | U20759 | 601199 | ARG67CYS  |
| Human parathyroid cell<br>calcium-sensing<br>receptor mRNA,<br>complete cds | U20759 | 601199 | PHE788CYS |
| Human parathyroid cell<br>calcium-sensing<br>receptor mRNA,<br>complete cds | U20759 | 601199 | LYS47ASN  |
| Human parathyroid cell<br>calcium-sensing<br>receptor mRNA,<br>complete cds | U20759 | 601199 | A986S     |

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|                                                      |        |        |               |                                              |
|------------------------------------------------------|--------|--------|---------------|----------------------------------------------|
| calcium-sensing<br>receptor mRNA,<br>complete cds    | U43148 | 601309 | 1148G-A       |                                              |
| Human patched<br>homolog (PTC)<br>mRNA, complete cds | U43148 | 601309 | 1-BP DEL      |                                              |
| Human patched<br>homolog (PTC)<br>mRNA, complete cds | U43148 | 601309 | 1-BP INS      |                                              |
| Human patched<br>homolog (PTC)<br>mRNA, complete cds | U43148 | 601309 | 11-BP DEL     | frameshift                                   |
| Human patched<br>homolog (PTC)<br>mRNA, complete cds | U43148 | 601309 | 2-BP INS      |                                              |
| Human patched<br>homolog (PTC)<br>mRNA, complete cds | U43148 | 601309 | 3340A-T       |                                              |
| Human patched<br>homolog (PTC)<br>mRNA, complete cds | U43148 | 601309 | 37-BP DEL     |                                              |
| Human patched<br>homolog (PTC)<br>mRNA, complete cds | U43148 | 601309 | 451C-T        | Pro-Ser                                      |
| Human patched<br>homolog (PTC)<br>mRNA, complete cds | U43148 | 601309 | 9-BP INS      | CODON 815,<br>PRO-ASN-ILE<br>INS<br>nonsense |
| Human patched<br>homolog (PTC)<br>mRNA, complete cds | U43148 | 601309 | CAG to TAG at |                                              |

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|                                                                                          |        |        |            |           |
|------------------------------------------------------------------------------------------|--------|--------|------------|-----------|
| homolog (PTC)<br>mRNA, complete cds                                                      |        |        | codon 361  |           |
| Human patched<br>homolog (PTC)                                                           | U43148 | 601309 |            | GLN210TER |
| mRNA, complete cds                                                                       |        |        |            |           |
| Human patched<br>homolog (PTC)                                                           | U43148 | 601309 |            | Gln816Leu |
| mRNA, complete cds                                                                       |        |        |            |           |
| Human PTH2<br>parathyroid hormone<br>receptor mRNA,<br>complete cds                      | U25128 | 601469 | none found |           |
| Human putative<br>calcium influx channel<br>(htrp3) mRNA,<br>complete cds                | U47050 | 602345 | none found |           |
| Human receptor for<br>advanced glycosylation<br>end products (RAGE)<br>mRNA, partial cds | M91211 | 600214 | none found |           |
| Human serum vitamin<br>D-binding protein<br>(hDBP) mRNA,<br>complete cds                 | M12654 | 139200 | HaeIII     |           |
| Human serum vitamin<br>D-binding protein<br>(hDBP) mRNA,<br>complete cds                 | M12654 | 139200 | (TAAA)n    |           |
| Human serum vitamin<br>D-binding protein<br>(hDBP) mRNA,                                 | M12654 | 139200 | MspI       |           |

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|                                                                 |        |        |                  |           |
|-----------------------------------------------------------------|--------|--------|------------------|-----------|
| complete cds                                                    |        |        |                  |           |
| Human serum vitamin D-binding protein (hDBP) mRNA, complete cds | M12654 | 139200 | Styl             |           |
| Human serum vitamin D-binding protein (hDBP) mRNA, complete cds | M12654 | 139200 | T to C at Cys283 |           |
| Human serum vitamin D-binding protein (hDBP) mRNA, complete cds | M12654 | 139200 |                  | THR420LYS |
| Human somatostatin I gene and flanks                            | J00306 | 182450 | BamHI intron     |           |
| Human somatostatin I gene and flanks                            | J00306 | 182450 | EcoRI 3'         |           |
| Human SREBP-1 mRNA, complete cds                                | U00968 | 184756 | none found       |           |
| Human stanniocalcin mRNA, complete cds                          | U46768 | 601185 | none found       |           |
| Human steroid 5-alpha-reductase 2 (SRD5A2) mRNA, complete cds   | M74047 | 264600 | 1-BP DEL         | PRO251DEL |
| Human steroid 5-alpha-reductase 2 (SRD5A2) mRNA, complete cds   | M74047 | 264600 | null allele      |           |
| Human steroid 5-alpha-reductase 2 (SRD5A2) mRNA, complete cds   | M74047 | 264600 |                  | ARG246TRP |
| Human steroid 5-alpha-reductase 2 (SRD5A2) mRNA, complete cds   | M74047 | 264600 |                  | GLY115ASP |

|                                                                                 |        |        |                  |
|---------------------------------------------------------------------------------|--------|--------|------------------|
| reductase 2 (SRD5A2)<br>mRNA, complete cds                                      | M74047 | 264600 | GLY183SER        |
| Human steroid 5-alpha-<br>reductase 2 (SRD5A2)<br>mRNA, complete cds            | M74047 | 264600 | GLY196SER        |
| Human steroid 5-alpha-<br>reductase 2 (SRD5A2)<br>mRNA, complete cds            | M74047 | 264600 | HIS231ARG        |
| Human steroid 5-alpha-<br>reductase 2 (SRD5A2)<br>mRNA, complete cds            | M74047 | 264600 | LEU55GLN         |
| Human steroid 5-alpha-<br>reductase 2 (SRD5A2)<br>mRNA, complete cds            | M74047 | 264600 | MET157DEL        |
| Human steroid 5-alpha-<br>reductase 2 (SRD5A2)<br>mRNA, complete cds            | M74047 | 264600 | THR228ALA        |
| Human steroid 5-alpha-<br>reductase 2 (SRD5A2)<br>mRNA, complete cds            | M74047 | 264600 | ARG227TER        |
| Human steroidogenic<br>acute regulatory<br>protein (StAR) mRNA,<br>complete cds | U17280 | 600617 | 840delA          |
| Human steroidogenic<br>acute regulatory<br>protein (StAR) mRNA,<br>complete cds | U17280 | 600617 | IVS4AS, T-A, -11 |

|                                                                                       |        |        |                       |
|---------------------------------------------------------------------------------------|--------|--------|-----------------------|
| Human steroidogenic acute regulatory protein (StAR) mRNA, complete cds                | U17280 | 600617 | GLN258TER             |
| Human steroidogenic acute regulatory protein (StAR) mRNA, complete cds                | U17280 | 600617 | ARG182LEU             |
| Human steroidogenic acute regulatory protein (StAR) mRNA, complete cds                | U17280 | 600617 | 1-BP DEL, 261T        |
| Human steroidogenic acute regulatory protein (StAR) mRNA, complete cds                | U17280 | 600617 | IVS2, 1-BP INS, T, +3 |
| Human steroidogenic acute regulatory protein (StAR) mRNA, complete cds                | U17280 | 600617 | D203A                 |
| Human sterol regulatory element binding protein-2 mRNA, complete cds                  | U02031 | 600481 | none found            |
| Human transforming growth factor-beta type III receptor (TGF-beta) mRNA, complete cds | L07594 | 600742 | none found            |
| Human type II iodothyronine deiodinase mRNA,                                          | U53506 | 601413 | none found            |

|                                                                                             |        |        |                     |           |
|---------------------------------------------------------------------------------------------|--------|--------|---------------------|-----------|
| complete cds                                                                                | U20165 | 600799 | none found          |           |
| Human type II<br>serine/threonine kinase<br>receptor mRNA,<br>complete cds                  | U43142 | 601528 | none found          |           |
| Human vascular<br>endothelial growth<br>factor related protein<br>VRP mRNA, complete<br>cds | U43368 | 601398 | none found          |           |
| Human VEGF related<br>factor isoform VRF186<br>precursor (VRF)                              | M67466 | 201810 | 1-BP INS            |           |
| mRNA, complete cds                                                                          |        |        |                     |           |
| Hydroxy-delta-5-<br>steroid dehydrogenase,<br>3 beta- and steroid<br>delta-isomerase 2      | M67466 | 201810 | Dinucleotide repeat |           |
| Hydroxy-delta-5-<br>steroid dehydrogenase,<br>3 beta- and steroid<br>delta-isomerase 2      | M67466 | 201810 |                     | ARG249TER |
| Hydroxy-delta-5-<br>steroid dehydrogenase,<br>3 beta- and steroid<br>delta-isomerase 2      | M67466 | 201810 |                     | VAL248ASN |
| Hydroxy-delta-5-<br>steroid dehydrogenase,<br>3 beta- and steroid<br>delta-isomerase 2      | M67466 | 201810 |                     | TRP171TER |

|                                                                    | Accession | Gene             | Chromosome | Position | RefSeq ID | Protein | Mutation | Effect                                   | Notes          |
|--------------------------------------------------------------------|-----------|------------------|------------|----------|-----------|---------|----------|------------------------------------------|----------------|
| steroid dehydrogenase,<br>3 beta- and steroid<br>delta-isomerase 2 |           |                  |            |          |           |         |          |                                          |                |
|                                                                    |           |                  |            |          |           |         |          |                                          |                |
|                                                                    |           |                  |            |          |           |         |          |                                          |                |
|                                                                    |           |                  |            |          |           |         |          |                                          |                |
|                                                                    |           |                  |            |          |           |         |          |                                          |                |
|                                                                    |           |                  |            |          |           |         |          |                                          |                |
|                                                                    |           |                  |            |          |           |         |          |                                          |                |
|                                                                    |           |                  |            |          |           |         |          |                                          |                |
|                                                                    |           |                  |            |          |           |         |          |                                          |                |
|                                                                    |           |                  |            |          |           |         |          |                                          |                |
| hyrotropin beta (TSH-<br>beta)                                     | M21023    |                  |            |          |           |         |          | none found                               |                |
|                                                                    | Y00285    | IGF-2 receptor   |            | 147280   |           |         |          | 17 bp deletion                           |                |
|                                                                    | Y00285    | IGF-2 receptor   |            | 147280   |           |         |          | CA repeat polymorphisms                  |                |
|                                                                    | Y00285    | IGF-2 receptor   |            | 147280   |           |         |          | SacI                                     |                |
|                                                                    | Y00285    | IGF-2 receptor   |            | 147280   |           |         |          |                                          |                |
|                                                                    | Y00285    | IGF-2 receptor   |            | 147280   |           |         |          |                                          |                |
|                                                                    | M10051    | Insulin receptor |            | 147670   |           |         |          | 10 base pair deletion                    |                |
|                                                                    | M10051    | Insulin receptor |            | 147670   |           |         |          | 1058 CAC-->CAT                           |                |
|                                                                    | M10051    | Insulin receptor |            | 147670   |           |         |          | 12 additional base pairs in exon 3       |                |
|                                                                    | M10051    | Insulin receptor |            | 147670   |           |         |          | 3' flanking intron (T->G at position 74) |                |
|                                                                    | M10051    | Insulin receptor |            | 147670   |           |         |          | 400-bp insertion intron                  |                |
|                                                                    | M10051    | Insulin receptor |            | 147670   |           |         |          | 8-BP DEL                                 |                |
|                                                                    | M10051    | Insulin receptor |            | 147670   |           |         |          | A-G, -2 intron 4                         |                |
|                                                                    | M10051    | Insulin receptor |            | 147670   |           |         |          | Alu                                      |                |
|                                                                    | M10051    | Insulin receptor |            | 147670   |           |         |          | codon 1058 (CAC-->CAT)                   | lys1030 silent |
|                                                                    | M10051    | Insulin receptor |            | 147670   |           |         |          | deletion of the gene                     |                |
|                                                                    | M10051    | Insulin receptor |            | 147670   |           |         |          | EcoRI                                    |                |
|                                                                    | M10051    | Insulin receptor |            | 147670   |           |         |          | EX14DEL                                  |                |
|                                                                    | M10051    | Insulin receptor |            | 147670   |           |         |          | Four RSAI                                |                |
|                                                                    | M10051    | Insulin receptor |            | 147670   |           |         |          | G-->T at position 13, 5' intron          |                |

|                  |        |        |                           |            |
|------------------|--------|--------|---------------------------|------------|
| Insulin receptor | M10051 | 147670 | Gln276 (CAA-->CAG)        | silent     |
| Insulin receptor | M10051 | 147670 | Gly8 (GGA-->GGG)          | silent     |
| Insulin receptor | M10051 | 147670 | His1068 (CAC-->CAT)       | silent     |
| Insulin receptor | M10051 | 147670 | Insertion intron 9,       |            |
| Insulin receptor | M10051 | 147670 | Nsil                      |            |
| Insulin receptor | M10051 | 147670 | Nsil                      |            |
| Insulin receptor | M10051 | 147670 | Short repeats in intron 2 |            |
| Insulin receptor | M10051 | 147670 | Thr789 (ACG-->ACA)        | silent     |
| Insulin receptor | M10051 | 147670 |                           | GLY996VAL  |
| Insulin receptor | M10051 | 147670 |                           | GLU672TER  |
| Insulin receptor | M10051 | 147670 |                           | LYS460GLU  |
| Insulin receptor | M10051 | 147670 |                           | Asn461Thr  |
| Insulin receptor | M10051 | 147670 |                           | MET1153ILE |
| Insulin receptor | M10051 | 147670 |                           | ARG86PRO   |
| Insulin receptor | M10051 | 147670 |                           | TRP1200SER |
| Insulin receptor | M10051 | 147670 |                           | TRP?SER    |
| Insulin receptor | M10051 | 147670 |                           | ALA1134THR |
| Insulin receptor | M10051 | 147670 |                           | LYS121TER  |
| Insulin receptor | M10051 | 147670 |                           | ILE119MET  |
| Insulin receptor | M10051 | 147670 |                           | ARG735SER  |
| Insulin receptor | M10051 | 147670 |                           | ARG981GLN  |
| Insulin receptor | M10051 | 147670 |                           | ARG988TER  |
| Insulin receptor | M10051 | 147670 |                           | TRP412SER  |
| Insulin receptor | M10051 | 147670 |                           | ALA1135GLU |
| Insulin receptor | M10051 | 147670 |                           | ARG1000TER |
| Insulin receptor | M10051 | 147670 |                           | ASN462SER  |
| Insulin receptor | M10051 | 147670 |                           | CODON 897  |

|                                       |        |        |             |
|---------------------------------------|--------|--------|-------------|
| Insulin receptor                      | M10051 | 147670 | nonsense    |
| Insulin receptor                      | M10051 | 147670 | HIS209ARG   |
| Insulin receptor                      | M10051 | 147670 | TRP133TER   |
| Insulin receptor                      | M10051 | 147670 | Asn281del   |
| Insulin receptor                      | M10051 | 147670 | his252arg   |
| Insulin receptor                      | M10051 | 147670 | Leu999del   |
| Insulin receptor                      | M10051 | 147670 | glyc1008val |
| Insulin receptor                      | M10051 | 147670 | glu1131arg  |
| Insulin receptor                      | M10051 | 147670 | Leu193Pro   |
| Insulin receptor                      | M10051 | 147670 | ser462asp   |
| Insulin receptor                      | M10051 | 147670 | GLY31ARG    |
| Insulin receptor                      | M10051 | 147670 | PHE382VAL   |
| Insulin receptor                      | M10051 | 147670 | LEU233PRO   |
| Insulin receptor                      | M10051 | 147670 | Arg86ter    |
| Insulin receptor                      | M10051 | 147670 | Trp1193Leu  |
| Insulin receptor                      | M10051 | 147670 | Leu1178Pro  |
| Insulin receptor                      | M10051 | 147670 | ARG1174GLN  |
| Insulin receptor                      | M10051 | 147670 | VAL985MET   |
| Insulin receptor                      | M10051 | 147670 | GLY366ARG   |
| Insulin receptor                      | M10051 | 147670 | VAL28ALA    |
| Insulin receptor                      | M10051 | 147670 | Asp59Gly    |
| Insulin receptor                      | M10051 | 147670 | Leu62Pro    |
| Insulin receptor                      | M10051 | 147670 | ARG372TER   |
| Insulin receptor                      | M10051 | 147670 | ASN15LYS    |
| Insulin receptor                      | M10051 | 147670 | ARG1152GLN  |
| Insulin-like growth factor 1 receptor | X04434 | 147370 | none found  |
| Insulin-like growth factor 2          | J03242 | 147470 | (CA)n       |
| Insulin-like growth factor 2          | J03242 | 147470 | Apal 3'UTR  |

|                                              |           |        |                   |
|----------------------------------------------|-----------|--------|-------------------|
| Insulin-like growth factor 2                 | J03242    | 147470 | Avall             |
| Insulin-like growth factor 2                 | J03242    | 147470 | BamHI             |
| Insulin-like growth factor 2                 | J03242    | 147470 | Eco RI            |
| Insulin-like growth factor 2                 | J03242    | 147470 | Sst I             |
| Insulin-like growth factor 2                 | J03242    | 147470 | VNTR upstream     |
| insulin-like growth factor binding protein 1 | NM_000596 | 146730 | none found        |
| Insulin-like growth factor1                  | M29644    | 147440 | (CA)n             |
| Insulin-like growth factor1                  | M29644    | 147440 | EcoRV             |
| Insulin-like growth factor1                  | M29644    | 147440 | EX4,5 DEL         |
| Insulin-like growth factor1                  | M29644    | 147440 | HindIII           |
| Insulin-like growth factor1                  | M29644    | 147440 | PvuII             |
| interleukin 1 receptor (IL-1R)               | M27492    | 147810 | PstI              |
| interleukin 6 receptor (IL-6R) (20)          | M20566    | 147880 | dinucleotide (CA) |
| inward rectifier K channel                   | D50582    |        | none found        |
| leptin receptor/LEPR                         | NM_002303 | 601007 | (CTTTA)n          |
| leptin receptor/LEPR                         | NM_0023   | 601007 | 3'-UTR            |

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